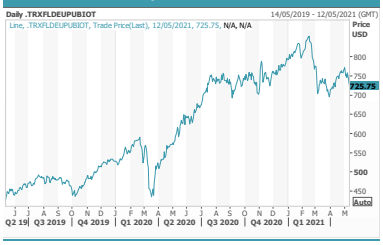
Biotech Europe index



Source: Refinitiv

Market data

EPIC/TKR	**CIZ**
Price (p)	**10.0**
12m high (p)	-
12m low (p)	-
Shares (m)	261.1
Mkt cap (£m)	26.1
EV (£m)	24.4
Free float	73%
Country of listing	UK
Market	LSE Main

Description

Cizzle is a medical device company developing a companion diagnostic biomarker for the early detection of lung cancer. The blood test will be used alongside a positive chest scan to confirm presence of lung cancer and reduce the high rate of false positives.

Company information

Executive Chair	Allan Syms
NED/Founder	Dawn Coverley
CFO	Nigel Lee
NED	John Treacy

www.cizzlebiotechnology.com

Key shareholders

Directors	5.1%
Yorkshire Cancer Research	12.4%
Finance Yorkshire	9.4%
Rose Noble Ltd	5.8%
University of Sheffield	4.3%
University of Leeds	4.3%

Diary

14 May	Admission to LSE

Analyst

Martin Hall 020 3693 7075

mh@hardmanandco.com

CIZZLE BIOTECHNOLOGY/BOULD

Early detection of lung cancer

Cizzle Biotechnology Ltd (Cizzle) was identified by Bould Opportunities (Bould) as its preferred target for a reverse takeover. Cizzle is a spin-out from the University of York to exploit the biomarker, variant CIZ1b, for early detection of different forms of lung cancer. The presence of nodules often detected on chest scans is suspicious, but not usually a sign of lung disease. Therefore, there is high medical need for a simple blood test to be used alongside a positive chest scan that allows early detection of lung cancer and significantly reduces the number of false positives. The company has raised £2.2m to develop its biomarker test through to CE marking.

- **Strategy:** Cizzle is a diagnostic company progressing a biomarker companion diagnostic assay that aims to deliver a simple blood test for lung cancer which can pick up the disease earlier to improve the chances of survival, and to greatly reduce the need for unnecessary follow-up tests and tissue biopsies.

- **Variant CIZ1b:** CIZ1 is a naturally occurring cell nuclear protein that promotes DNA replication. Cizzle has shown that variant CIZ1b is prevalent in lung tumours. The variant protein can be detected in the blood at an early stage in lung cancer patients, when the disease still bears a good prognosis.

- **The opportunity:** Lung cancer is generally first identified from a chest scan. Patients with suspicious scans then undergo further tests. However, these often result in false positives that require two-year follow-up. Eliminating 50% of these could help patients and generate substantial cost savings for healthcare providers.

- **Risks:** Cizzle has a proven prototype test. To move this to a commercial product with CE marking, the company needs to produce a monoclonal antibody, optimise the reagents and buffer environment, and validate the test with a retrospective trial. The aim is to achieve this within two years.

- **Investment summary:** The EV of Cizzle, at the time of Admission, will be £24.4m. A group of four close peers, all working in the field of specialist diagnostics/liquid biopsies, mostly in the field of oncology, currently have an average EV of £109.2m, but are at a later stage of development and/or involved in COVID-19 testing. This suggests that Cizzle is trading at a discount of 78% to its peers, reflecting its earlier stage of development, with considerable upside potential.

Financial summary and valuation

Year-end Dec (£000)	2017	2018	2019	2020E	2021E	2022E
Sales	0	0	0	0	0	0
COGS	-74	0	0	0	0	0
SG&A	-68	-54	-22	-15	-300	-500
R&D	0	0	0	0	-250	-500
Underlying EBIT	-140	-3	-22	-15	-570	-1,050
Reported EBIT	-140	-3	-22	-15	-1,380	-1,050
Underlying PBT	-140	-3	-22	-15	-570	-1,050
Statutory PBT	-140	-3	-22	-15	-1,380	-1,050
Underlying EPS (p)	-37.6	-0.9	-6.9	-4.8	-0.3	-0.4
Statutory EPS (p)	-37.6	-0.9	-6.9	-4.8	-0.8	-0.4
Net (debt)/cash	13	20	13	0	1,290	425
Equity issues	0	0	0	0	2,200	0

Source: Hardman & Co Life Sciences Research

Table of contents

Executive summary

Background

CIZ1 is a protein found in all human cells important for DNA replication

Cdkn1A-interacting zinc finger protein 1 (CIZ1) is a naturally occurring cell nuclear protein that promotes DNA replication, and has been found to be altered in many common cancers. The volume of research on this protein is relatively limited, but much of the work has emanated from the Mammalian Cell Cycle Research Group, in the Department of Biology at the University of York, under the leadership of Professor Dawn Coverley. Most of the academic research to elucidate the role of CIZ1 in the body has been undertaken in her research group, which is largely grant-funded, while the understanding of variants of CIZ1 and the potential to develop diagnostic cancer tests have been undertaken within Cizzle Biotech with investment funding.

Integrating academic and private research

Mammalian Cell Cycle Research Group, University of York	Cizzle Biotech Ltd
Grant-funded academic research	Investment-funded R&D
• Function of CIZ1 in normal cells	• Expression of CIZ1 variants in cancer
• Biological context	• Variant CIZ1b
• Profiling CIZ1 variants	• Diagnostic test based on CIZ1b

Source: Prof. Dawn Coverley, Hardman & Co Life Sciences Research

Cizzle looking to optimise its prototype test to commercial test for early-stage lung cancer

Cizzle is now ready to move to the next stage, converting its proof-of-principle prototype test to a commercial monoclonal antibody-based test for the accurate diagnosis of early-stage lung cancer.

Importance of CIZ1

CIZ1 is a protein comprised of 898 amino acid residues, which is found in the cell nucleus, and has been shown to play a role in DNA replication and cell cycle regulation. A prerequisite for the health and longevity of multicellular organisms is the precise duplication of the genome. This requires a high level of precision to ensure that DNA replication occurs once, and only once, per cell cycle. Crucially, the proteins that are associated with DNA must also be copied accurately. When something goes wrong in this complex process, biological dysfunction results.

Simplistic schematic of CIZ1 protein

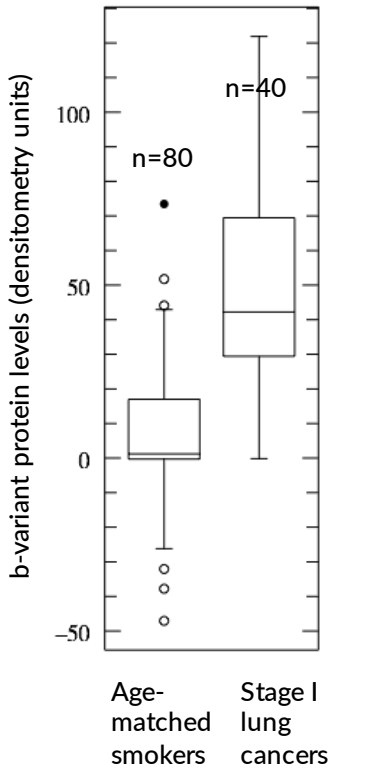
Source: Cizzle

Through deletion, overexpression or alternative splicing, CIZ1 is associated with tumour growth in a number of organs, particularly the lung. Recently, some variants of CIZ1 have been defined, which have resulted in significant loss of amino acid residues in different locations on the CIZ1 protein. Some of these are disease-specific and Cizzle has shown that variant CIZ1b is prevalent in lung tumours. Variant CIZ1b lacks eight amino acids from its nuclear matrix anchor domain (14-15).

Prototype diagnostic

With this knowledge, Cizzle has developed a quantitative immunoassay for measuring the CIZ1b biomarker in plasma taken from lung cancer patients. The prototype test, based on a technique called Western blot (WB), has been proven in 486 plasma samples derived from four independent sample sets including samples from patients with different types of lung cancer, asthma/COPD, and those who are heavy smokers (Results from Cohort 2 are shown in the margin graphic).

Test results from cohort 2



Source: Cizzle

Key steps are generation of a mAb, test refinement and CE marking

Cizzle has demonstrated that it has a test that can select a positive patient, but this is not considered sufficiently reliable for a high-throughput application in a hospital setting. Therefore, the objective now is to refine the test to generate one that would be suitable for commercial scale-up and kit manufacture. Over the next two years, Cizzle is aiming to:

- replace the WB method by the more appropriate enzyme-linked immunosorbent assay (ELISA)-monoclonal antibody (mAb) technique;
- refine the reagents so that the buffer environment is optimised for the ELISA test; and
- undertake a confirmatory trial to validate the test in order to get CE marking.

Diagnosis of lung cancer

Extensive data indicate that lung cancer is generally diagnosed when late-stage…

Both Cancer Research UK and the US National Cancer Institute (NCI) have data to show that about three quarters of patients are diagnosed at a late stage (72%-76% are diagnosed at stage III or IV), whereas one quarter are diagnosed at an early stage (24%-28% at stage I or II). Therefore, most people are diagnosed at a stage where prognosis is poor, as evidenced by the US five-year survival data of just 19.4%.

…leading to poor five-year survival statistics

One reason for this is that diagnosis of lung cancer is an extremely complex process. Patients usually go to their GP with a range of symptoms, which, after considering the history of smoking and family history, may result in a referral of the patient to the chest clinic, triggering a complex treatment pathway, usually resulting in a chest X-ray (CXR) or a chest computerised tomography (CT) scan. Even after a positive scan, the patient will undergo further tests.

Ambiguous and false positive chest scans require two-year follow-up of more scans or tissue biopsy…

Because it is simpler, most suspected lung cancer patients will undergo another scan. However, it is estimated that 90% of people having a confirmatory scan due to the presence of a size-qualifying nodule do not actually have lung cancer. In addition, all of these cases will be monitored for up to two years, with chest CT scans every six months, which represents an enormous burden for the healthcare system.

…highlighting need for simple confirmatory diagnostic test

Therefore, there is a significant medical need for a simple confirmatory test for lung cancer, which can pick up the disease much earlier to improve the chances of survival, and to reduce significantly the need for unnecessary follow-up chest CT scans for two years. Cizzle hopes to fulfil this niche with a simple blood test.

Health economics

Cizzle's test would reduce burden on health systems and make considerable savings for healthcare providers…

Based on accurate data for the number of chest CT scans performed in the UK, coupled with the actual number of lung cancer patients diagnosed, it is possible to calculate the potential savings to the NHS. On the assumption that the Cizzle biomarker test would cost £200, the annual sales potential would be £20.7m. However, removing 50% of the false positives from the two-year follow-up process would result in 207,400 fewer chest CT scans being performed, saving the NHS £83.0m, generating net savings of £62.3m over a two-year period.

…for example, £62.3m (net) for the NHS and ca.$230m in the US over a two-year period

Applying the same calculations to the larger patient population in the US, and using a test cost of $400, the sales potential of the Cizzle biomarker would be ca.$115m and generate potential savings for the healthcare providers of ca.$230m over a two-year period.

Funding and readmission

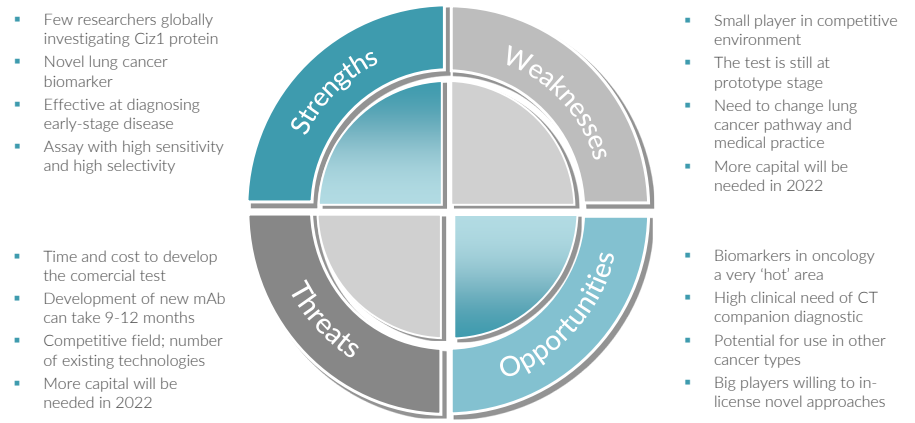
Prior to its suspension, Bould was listed as a cash shell on AIM. Following the acquisition of Cizzle, with the consideration being paid in new Ordinary shares, Bould has been admitted to trading on the Main Market of the London Stock Exchange and it is changing its name to Cizzle Biotechnology Holdings plc.

£2.2m of new funding will provide Cizzle with a cash runway of 18-24 months

Concomitantly, the company has undertaken a 1-for-500 share consolidation, and is raising £2.2m gross (£1.78m net) to fund the development of the commercial test through to CE marking. Cizzle will outsource most of its operating activities to experienced partners. Based on our forecasts for the enlarged entity, Cizzle will have a cash runway of 18-24 months.

SWOT analysis

SWOT analysis



Source: Hardman & Co Life Sciences Research

Valuation

On Admission, Cizzle will have EV of £24.4m…

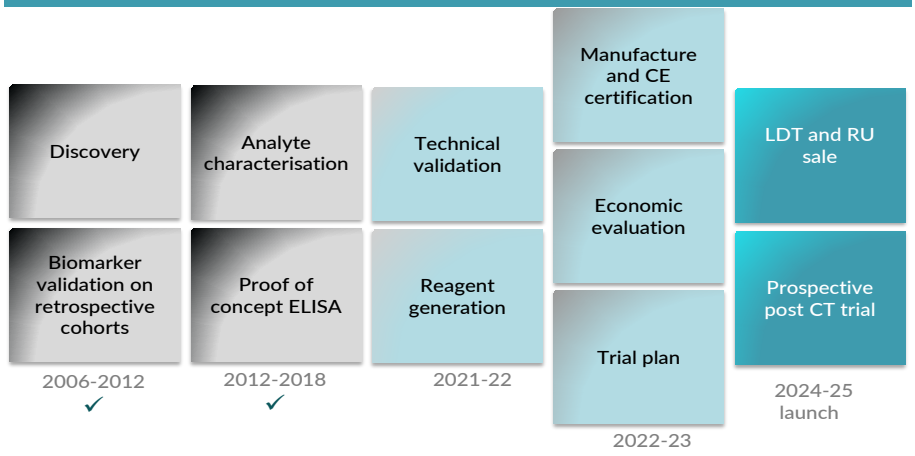
…which is a 78% discount to the average EV of four UK diagnostic peers, reflecting earlier stage of development

Both a DCF analysis and a peer group analysis have been used to generate a fair value for Cizzle alone. Readers should be made aware that a number of assumptions, albeit conservative, have been made in order to obtain these figures.

- The risk-adjusted DCF of the Cizzle platform technology generated a valuation of £21.7m.
- The average EV of UK diagnostic peers is currently £109.2m. On Admission, the enlarged entity had an EV of £24.4m suggesting that it will trade at a 78% discount to its peers, and reflecting its earlier stage of development. This suggests that, in the event that the test development progresses as planned, there should be considerable upside potential in Cizzle's EV.

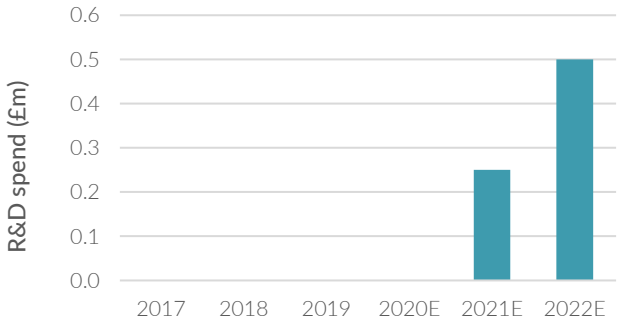
News flow

Development timelines



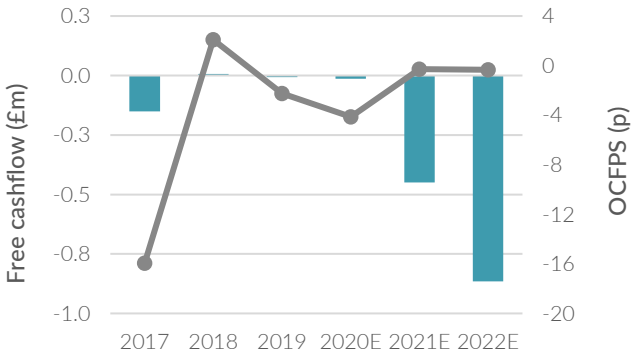
Source: Cizzle

R&D investment



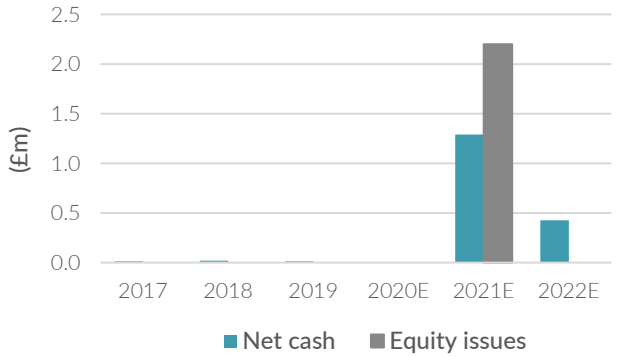
- Cizzle has successfully developed a prototype CIZ1b biomarker test on very limited resources.
- Much of the elucidation and understanding of CIZ1 was undertaken with grant funding.
- R&D investment will ramp up once funding is in place to develop the commercial CIZ1b biomarker test based on mAb direct-ELISA.

Free cashflow and OCFPS



- Cizzle will have two costs: R&D investment and the general corporate overhead.
- Some R&D tax credits can be expected, but payment by HMRC is usually six to 12 months in arrears.
- Given that much of the work will be outsourced, Cizzle will have only modest working capital requirements.

Net cash and equity issues



- The Admission document states that the *pro forma* net cash position will be £1.89m, but this is based on the balance sheets of both companies at 30 June 2020.
- After allowing for expenses associated with the acquisition, fund raise and listing, we believe the net cash position will be ca.£1.75m at the time of Admission.
- Forecasts suggest that this will provide a cash runway of 18-24 months and that further funds will be required towards the end of 2022.

Source: Company data; Hardman & Co Life Sciences Research

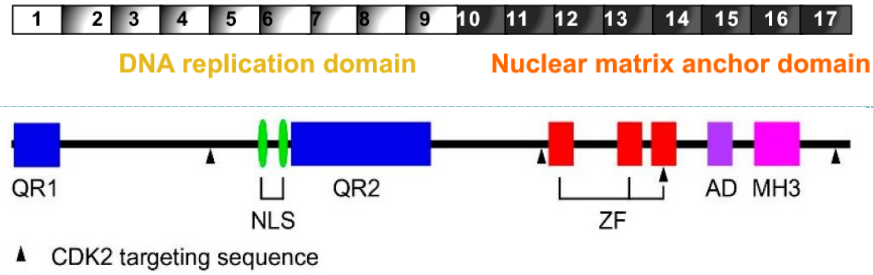
Elucidation of CIZ1 protein

Background

Cizzle's Science Director is a global expert on the CIZ1 protein with multiple peer-reviewed scientific publications

CIZ1 is a naturally occurring protein that was first described in 1999[1] and consists of an 898 amino acid residue chain in humans. There are relatively few research laboratories that have investigated the CIZ1 protein; however, much of the academic work to elucidate its normal function and its potential role in tumorigenesis (promoting cancer) has been undertaken by the Mammalian Cell Cycle Research Group, under the leadership of Professor Dawn Coverley. Cizzle Biotech evolved from this work to exploit and develop the intellectual property (IP).

Simplistic schematics of CIZ1 protein



Source: Cizzle, Liu et al[2]

- **Glutamine-rich domains (QR1 and QR2)** are not yet related to CIZ1's role in DNA replication. Abnormal expansion may lead to misfolding and aggregation of neurodegeneration-related proteins.
- One of the main functions of **Zinc-finger motifs (ZF)** is to bind nucleic acids.
- Various studies have shown that the **acid domain (AD)** is associated with a protein's stability and its ability to interact.
- The **MH3 domain** is found in matrin 3, a nuclear matrix protein, and NP220, a DNA-binding nuclear protein, suggesting that CIZ1 may bind to DNA or nuclear matrix-associated RNA.

Role in DNA replication

CIZ1 plays role in DNA replication and cell cycle regulation…

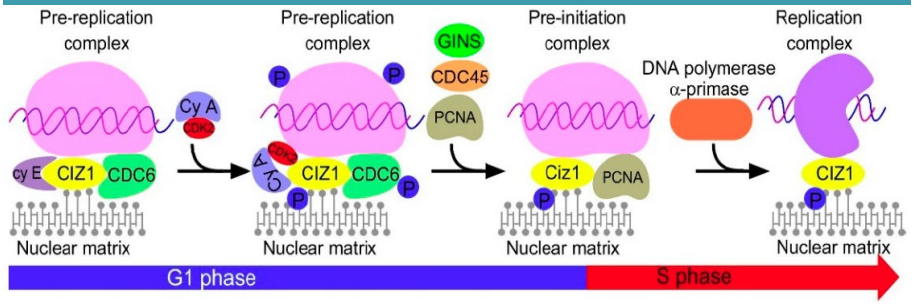
CIZ1 is a component of the cell nucleus and has been shown to play a role in DNA replication and cell cycle regulation. CIZ1 interacts with several proteins that contribute to the regulation of cellular proliferation (including transcriptional regulators), cell cycle regulators (including, among others, cyclin E, cyclin A and CDK2), and proteins that are not related directly to DNA replication[3]. Consequently, CIZ1 is considered to be involved in numerous biological functions.

Various experiments have been performed that support the hypothesis that CIZ1 plays a role in DNA replication:

- in both cell-free and cell-based experiments DNA replication can be stimulated by recombinant CIZ1; and
- the lack of CIZ1 has been shown to delay replication of DNA[4].

[1] Mitsui et al., 1999
[2] Liu et al., 2016
[3] Pauzaite et al., 2016
[4] Ainscough et al., 2007

Role of CIZ1 in DNA replication



Source: Liu et al[2]

Elucidating the function of CIZ1

A prerequisite for the health and longevity of multicellular organisms is the precise duplication of the genome. In order for this to occur, regulation of DNA replication is required prior to the genome segregating into daughter cells. This process is regulated at multiple levels to ensure near-perfect chromosome duplication, with error rates at less than one per billion bases copied[5]. This level of precision requires highly orchestrated and stratified mechanisms to ensure that DNA replication occurs once, and only once, per cell cycle. Crucially, the proteins that are associated with DNA and the chemical modifications that they bear must also be copied accurately. When something goes wrong in this complex process, biological dysfunction results.

…and variants of CIZ1 associated with different cancers…

Either through deletion, overexpression or alternative splicing, CIZ1 is associated with tumour growth in small cell (SCLC) and non-small cell lung cancer (NSCLC), colorectal, breast, prostate, hepatocellular carcinoma and gall bladder cancer, and lymphoma and leukaemia. In each case, there is a cancer-specific alteration resulting in the loss of, or increased, CIZ1 protein levels, or alternative splicing of the CIZ1 transcript.

CIZ1 associations in multiple cancers

Cancer type	CIZ1 alteration	Result of intervention
Lung	Alternative splicing – CIZ1b	Reduced tumour growth in xenograft models
Colorectal	Overexpression	Reduced proliferation, and colony formation *in vitro*
Gall blabber	Overexpression	Reduced xenograft tumour growth. Reduced tumour migration *in vivo*
Prostate	Overexpression	Reduced tumorigenesis in xenograft models. Reduced G1 checkpoint activation
Breast	Overexpression	Increased oestrogen sensitivity Increased tumour size in xenograft models
Hepatocellular	Overexpression	Increased proliferation, migration Primitive neuro ectodermal tumour

Source: Adapted from Pauzaite et al[3]

CIZ1 variants

Recently, a collection of mRNA variants of CIZ1 in humans, as a consequence of alternative splicing, have been defined, which have resulted in a significant loss of amino acid residues in different locations on the CIZ1 protein. Some of these have been shown to be disease-specific. For example, variant CIZ1ΔE4, in which exon 4 is omitted, is found in Ewing's tumour cells. Another splicing form, variant CIZ1b, has been shown to be prevalent in lung tumours, and this is the subject of Cizzle's IP. Thus, alternative splicing of CIZ1 seems to affect the biological function of CIZ1 in various pathological processes.

[5] Bebenek et al., 2004

Alternative splicing of CIZ1		
CIZ1 variants	Alternative splicing sites	Biological indication
CIZ1ΔE4	Exon 4	Ewing's tumour
CIZ1S	Partial exon 8	Alzheimer's disease
CIZ1M	Partial exon 8	Alzheimer's disease
CIZ1ΔE8-12	Exons 9, 10, 11; partial exons 8, 12	Ewing's tumour Primitive neuro ectodermal tumour
CIZ1b	Exon 14	Lung cancer

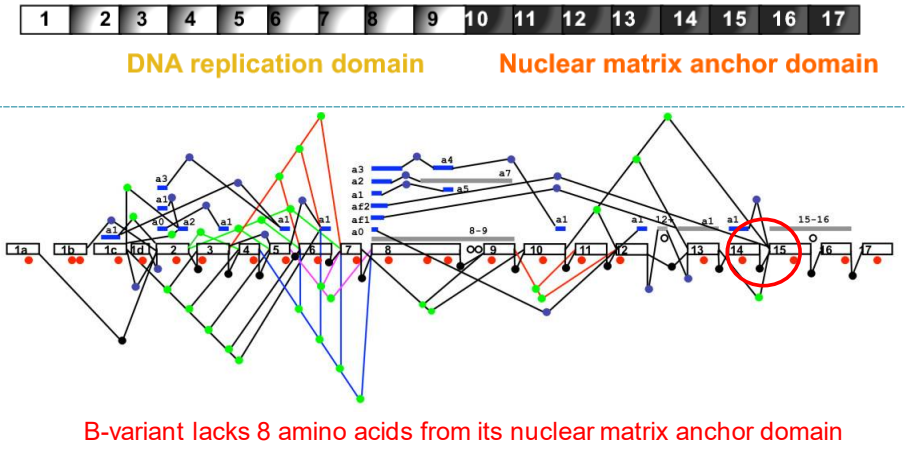
Source: Cizzle, Liu et al[2]

Variant CIZ1b

…with variant CIZ1b implicated specifically in lung cancer

The work of Cizzle has been concentrated on the cancer-specific CIZ1b variant that lacks eight amino acids from its nuclear matrix anchor domain, and is implicated in lung cancer.

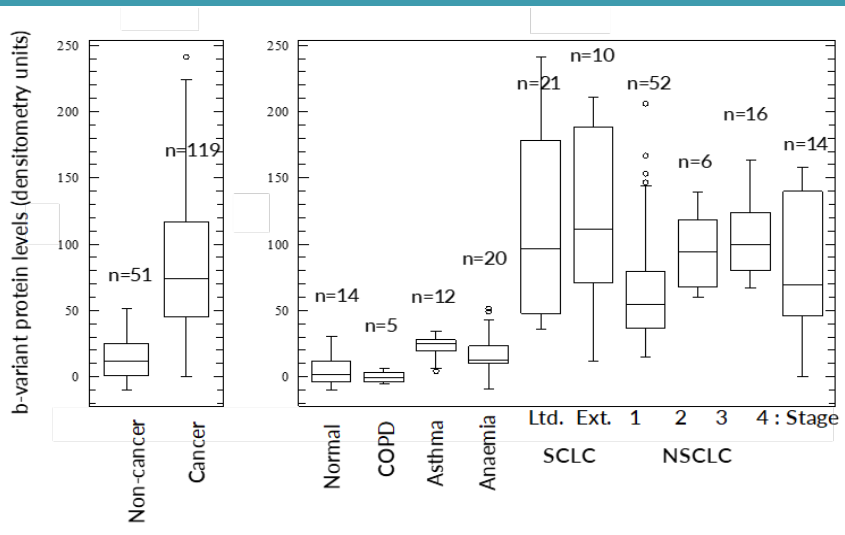
Schematic to show CIZ1b variant



Source: Rahman et al[6]

Development of CIZ1b diagnostic test

Test results from Cohort 1



Source: Cizzle

[6] Rahman et al., 2010

Cizzle has developed and validated an immunoassay for CIZ1b

Cizzle has developed a quantitative immunoassay for measuring the CIZ1b biomarker in plasma taken from lung cancer patients[7]. The prototype test, based on WB, has now been applied to 486 plasma samples, derived from four independent sample sets, including samples from patients with different types of lung cancer, asthma/COPD, and those who are heavy smokers. For Cohort 1, when thresholds are high, so that 98%-100% of cancer patients are detected, the false positive rate is 45%[8]. This is expected to be useful if applied after chest CT scans to exclude CT-false-positive patients. The sensitivity/false positive profile depends on where thresholds are set, and may differ with clinical context – for example, pre-CT screening, compared with post-CT validation.

[7] Coverley et al., 2017
[8] Higgins et al., 2012

Development of commercial test

Commercial scale-up

Next step is to convert prototype test into one that can be used commercially in high-throughput applications

As demonstrated in the previous section, Cizzle has developed and tested a prototype diagnostic test for lung cancer based on the CIZ1b biomarker using WB, with high sensitivity and a clinically useful false-positive rate. However, such a study simply indicates that you have a demonstrable test that has the ability to select a positive sample, but is less reliable when it comes to a high-throughput application in a hospital setting. The aim now is to refine the test to generate one that would be suitable for commercial scale-up and kit manufacture.

Comparison of WB with ELISA

Characteristic	WB	ELISA
Detection method	Immuno	Immuno
Sensitivity	High	High
Specificity	High	High
False positives	Potentially high	Potentially high
Quantification of specific protein	Can be poor	Good
Determine size of protein	Good	Very poor
Technical expertise needed	High level	Low level
Use in screening	Cumbersome	High throughput

Source: BioRad, Hardman & Co Life Sciences Research

What needs to be done?

Replacement of WB by ELISA-mAb

Key next step is to generate a mAb for the test…

Use of the WB technique needs to be changed to a sandwich ELISA test linked to a mAb (or synthetic alternative), which is a more standardised procedure that would reduce the technical demand and high cost associated with WB, making it more acceptable from a commercial standpoint.

…achievable, as demonstrated by generating a polyclonal version

The missing eight amino acids from the CIZ1b biomarker creates a unique junction against which an antibody can be formed. Cizzle knows that this is achievable having generated two polyclonal antibodies with the desired specificity, but this needs to be replaced by a mAb, the "b-variant capture antibody". Development of a specific mAb would provide a renewable reagent with surety of supply.

CIZ1b detection

Source: Cizzle

Detection would be made by an anti-fibrinogen antibody – the detector – which would be an off-the-shelf purchase. The CIZ1b biomarker in patient's plasma samples naturally exists attached to fibrinogen in the blood, producing a complex that can be detected by ELISA. Preliminary work showing that the fibrinogen can be detected by a sandwich ELISA with a similar sensitivity profile to WB has already been done[7].

Refinement of analytes/reagents

Associated with the change from WB to ELISA is the likely need to refine the analytical environment. Professor Coverley has demonstrated already that, depending on the detergents and reagents used in the process of sample preparation, in extreme conditions, the epitope (CIZ1b) can be lost. While proof-of-concept has been established, the buffer environment will need to be optimised for the ELISA test to suit the new reagent set.

Validatory trial

A validatory trial will be needed for CE marking and marketing literature

When the mAbs are available and the reagents/analytes optimised, a confirmatory trial will be needed to validate the test in order to get CE marking. Initially, this would be a retrospective study using samples with known clinical outcomes to obtain the test sensitivity and specificity claims that would be used in marketing literature. A trial similar to that reported by *Higgins et al* in 2012[8] is envisaged.

Intellectual property

Cizzle has a strong IP position around variant CIZ1b

Cizzle has protected the use of the b-variant (CIZ1b) biomarker for potential in the prognosis, diagnosis and therapy for a variety of cancers through a number of patents in key territories, including the US, China and the major European countries. Owing to a strategic and cost-cutting decision, patent WO2010089559, which was not focused on CIZ1b, has been abandoned.

Summary of Cizzle patent portfolio

Publication number	Priority date	Publication date	Status	Title
WO2004051269	12/05/2002	16/06/2004	Granted	CIZ1 replication protein
WO2010089559	05/02/2009	12/08/2010	Abandoned	Cancer diagnosis and treatment
WO2012017208	04/08/2010	09/02/2012	Granted	Methods and compounds for the diagnosis and treatment of cancer
WO2017068330	19/10/2015	27/04/2017	Prosecuting	Use of a fibrinogen capture agent to detect a CIZ1b-variant

Source: Cizzle, Hardman & Co Life Sciences Research

As Cizzle undertakes more work in developing the next-generation blood test with new reagents and new conditions, we can expect additional patents to be prosecuted to protect further the IP, thereby expanding the patent portfolio for the longer term.

Commercial opportunity

Sizing the opportunity

At the current time, tissue biopsy remains the gold-standard for confirming cancer diagnosis suspected from clinical symptoms and imaging. This allows pathologists to analyse complete cells within tumours. While tissue biopsy of cancerous tissues is essential in determining the type of cancer and guiding the immediate treatment regime, there is a strong need for early patient triage – i.e. is the nodule seen on the chest CT scan cancerous or not? This is crucial to minimise the potential for patient distress in an environment where CT imaging is being used more often, generating more patients who *might* have cancer but usually do not. However, getting to this stage is an onerous process and, in the case of lung cancer, when a confirmatory diagnosis is made, the stage of the cancer is often quite advanced. Therefore, the need for an accurate test that can detect early-stage lung cancer is a major medical need.

Current procedure

Diagnosis of lung cancer is an extremely complex process. Patients usually present to their general practitioner (GP) with one or more of the following symptoms:

- persistent cough;
- weight loss;
- coughing-up blood;
- chest pain; and/or
- chest infection that has failed to resolve.

Suspicious cases trigger a complex treatment pathway

The GP is likely to consider this to be high-risk and refer the patient to the chest clinic at the hospital, triggering a complex treatment pathway (see next page). About 70% of lung cancer patients are identified via this route. The other 30% are identified in the hospital setting via "incidental findings", whereby a patient attends A&E having already seen his/her GP and the problem has persisted, or the patient attends hospital for a completely different reason and something suspicious is found on a scan – usually a chest X-ray (CXR) or a chest CT.

Even after a positive scan, the patient is classified as "high clinical suspicion" requiring further tests. What happens next depends on local protocol, despite there being "National Optimal Lung Cancer Pathway" guidelines in place in many countries. However, the process will usually involve either another more detailed scan or a tissue biopsy, both of which can be upsetting for the patient and costly to the healthcare system.

Specific to lung cancer

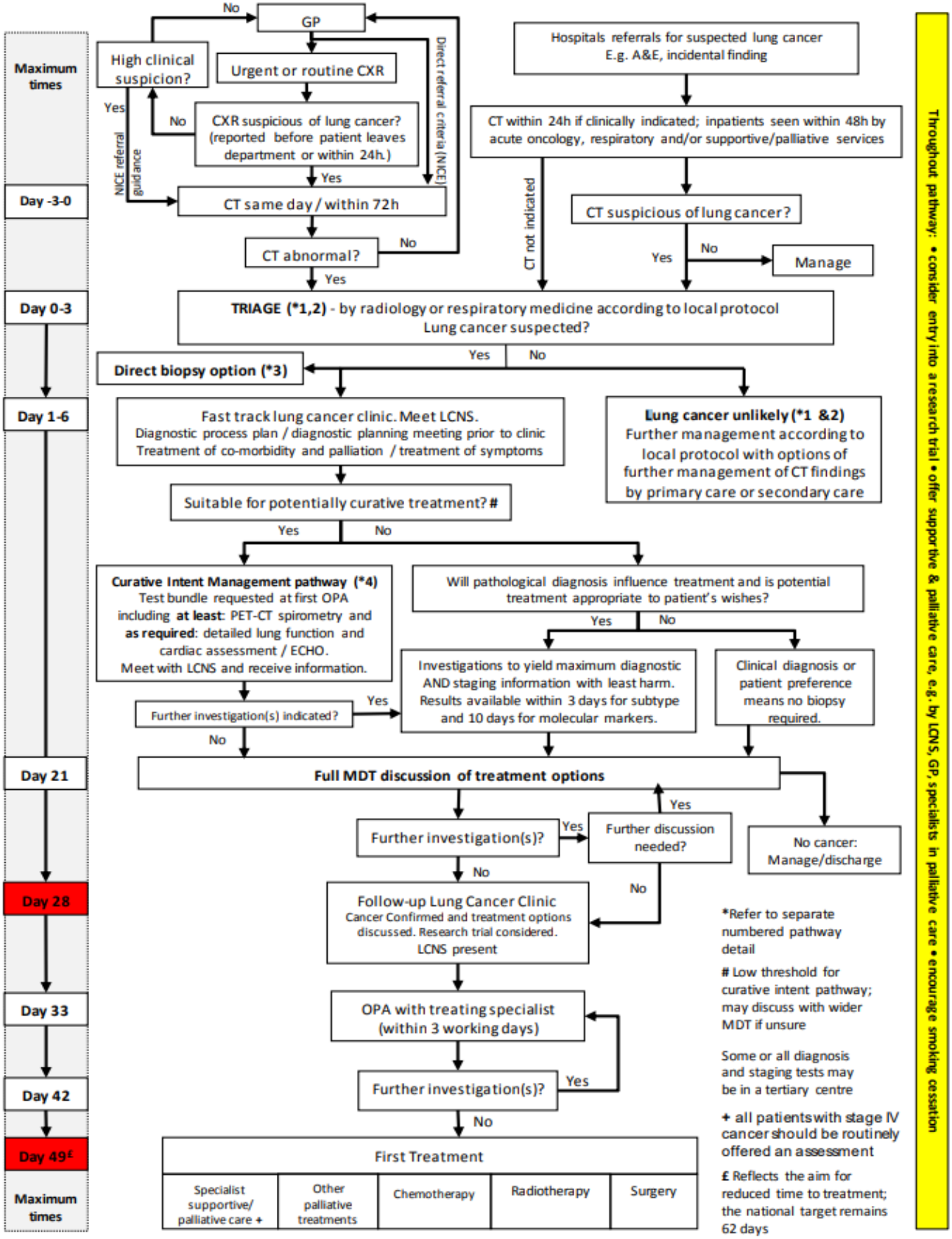
However, presence of large nodule rarely indicates lung cancer…

…leading to large number of false-positive results requiring follow-up scans

Because it is simpler, most suspected lung cancer patients will undergo another scan. However, it is estimated that 90% of people having a confirmatory scan due to the presence of a size-qualifying nodule do not actually have lung cancer. Also, for people that have CXR or CT scans for other reasons, about 13% of these have a size-qualifying nodule but 98% do not have cancer. Furthermore, all of these cases will be monitored for up to two years, with chest CT scans every six months. This represents a huge burden for the healthcare system, unnecessary overloading in lung cancer clinics and, importantly, upsetting patients that do not have cancer.

At the current time, tissue biopsy remains the standard-of-care to confirm the initial diagnosis, which allows pathologists to analyse complete cells within tumours. While tissue biopsy of cancerous tissues is essential in determining the type of cancer and guiding the immediate therapy regime, there is a strong need for early and accurate patient triage – i.e. is the nodule seen on the CXR or CT scan cancerous or not?

National Optimal Lung Cancer Pathway (UK)

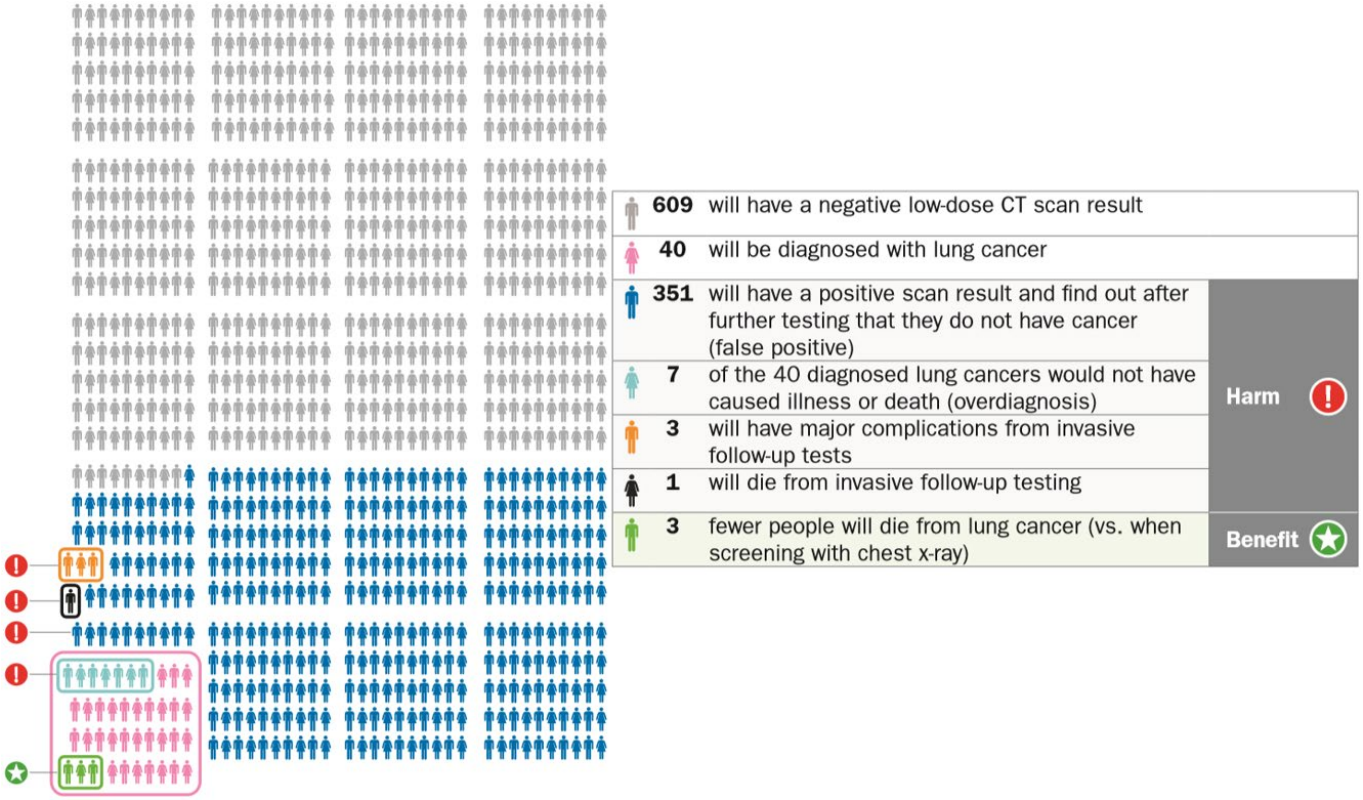


Source: Lung Clinical Expert Group, 2017

Real case scenario

A similar situation to that seen in the UK has been seen in Canada. The Canadian Task Force on Preventive Health Care[9] has also indicated that for every 1,000 people scanned annually for three years, 391 will show apparent indication of lung cancer. However, only 40 of those positive results are genuine. Of those 40, seven would not have died of the disease, and 30 would have died anyway – just three lives being saved. In addition, of the 391 that were showing apparent disease indication, four would suffer major complications, due to the diagnostic treatment, and one would die.

Screening 1,000 eligible people with CT



Source: Adapted from www. canadiantaskforce.ca; Hardman & Co Life Sciences Research

This highlights the poor screening standards that are in place for lung cancer, and the huge medical need for an accurate and reliable companion diagnostic tool to rule out misdiagnosed patients, with the economic benefits of saving costs and reducing pressure on healthcare systems.

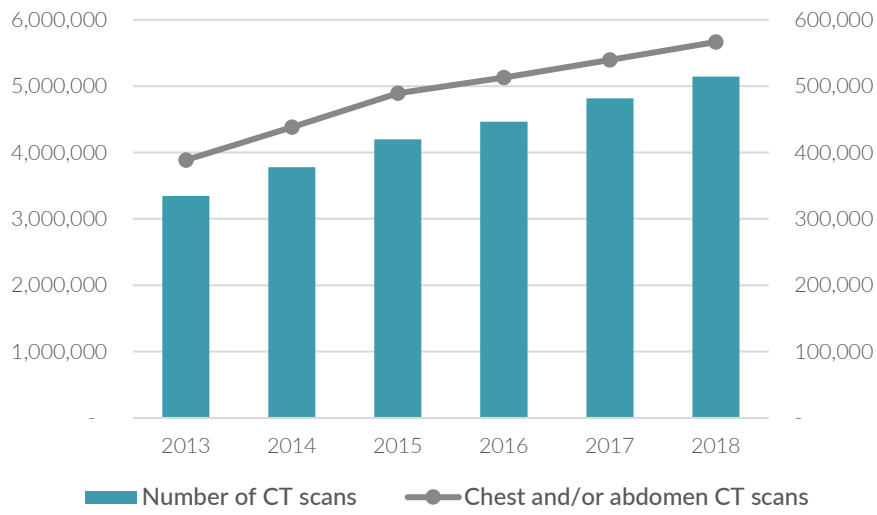
Clinical burden

A more accurate test would obviate need for repeat scans and take pressure off healthcare systems

To circumvent the misdiagnosis and late detection of lung cancer, there is a clear need for a much more efficient screening test that minimises false-positive interpretations. Usually, patients with size-qualifying nodules would be followed up for two years via a chest CT scan every six months, with each one taking ca.30 minutes to perform (10 minutes preparation + 15-20 minutes for the test). To put this in perspective, the number of CT scans performed in the NHS in the 12 months ending March 2019 was around 5.15m[10], and the five-year CAGR growth was 6.9%. Approximately 11% of these scans were for the chest and/or abdomen. Owing to the increased pressure on the scanners (and staff), the time taken from the date of request to the date of test averaged 16 days.

[9] Canadian Task Force on Preventive Healthcare
[10] NHS England – Diagnostic Imaging dataset

CT scans performed in the UK – 2013-18



Source: NHS England; Hardman & Co Life Sciences Research

Use of a suitable companion diagnostic tool/biomarker, alongside the CT scan to confirm/refute the malignant character of suspicious nodules would be beneficial for both the NHS and patients.

Cizzle opportunity

Simple, quick and accurate blood test for early detection and confirmation of lung cancer…

…that can also identify and eliminate at least 50% of false-positive patients

Cizzle is seeking to develop a simple, quick and accurate blood test for the early detection and confirmation of lung cancer. The aim is to develop a companion diagnostic tool to use alongside a CT scan in patients with suspected lung cancer that will help to eliminate false positives and remove patients that do not need follow-up scans for the next two years. Cizzle set up two strategic patient populations in this clinical niche:

- **Target 1:** for people having CT scans of the thorax for suspected lung cancer, who have a size-qualifying nodule (90% are not related to cancer); and
- **Target 2:** for people having CXR and CT scans for other reasons – about 13% of these have a size-qualifying nodule (98% are not related to cancer).

Based on previous work with its prototype WB diagnostic test, Cizzle estimates that it could safely exclude 50% of false-positive patients identified by CT.

Comparison with tissue biopsy

A diagnostic test, based on a small sample of blood has many advantages over invasive tissue biopsy:

- **Safety and invasiveness:** A simple blood draw, with only a small sample required, is routine and minimally invasive compared with the experience or invasive surgery.
- **Sampling:** Tumours in some locations may be difficult to reach in order to take a sample. Also, if insufficient tissue is taken, it is much easier to repeat a blood test than to repeat a tissue biopsy.
- **Timing:** A blood test can be scheduled quickly and performed at the same time as a scan, with results available the same day. In contrast, results from a tissue biopsy usually take a few days, delaying the onset of treatment, and are wrong in up to 20% of cases.
- **Use as companion diagnostic:** The effectiveness of lung resection in genuinely positive patients could potentially be monitored by redoing the biomarker test.

Lung cancer statistics

Background

Lung cancer characterised by detection at late stage...

...leading to poor five-year survival rates

In its early phase, lung cancer usually develops without any obvious symptoms and is difficult to detect with traditional radiographic methods, even to the trained eye. Even when there are symptoms, many people may mistake them for other problems such as a respiratory infection or the consequence of the long-term effects of smoking. Late detection is also caused by the lung not possessing pain receptors. Consequently, compared with other types of cancers, there has been little improvement in the survival rate for lung cancer in the past 25 years.

Lung cancer is divided into four stages, with stage I being localised to the lung through to stage IV where the cancer has metastasised into distant organs. Given the late detection and the complex optimal lung cancer care pathway described earlier, the overall prognosis is poor, making it one of the leading causes of death.

Types of lung cancer

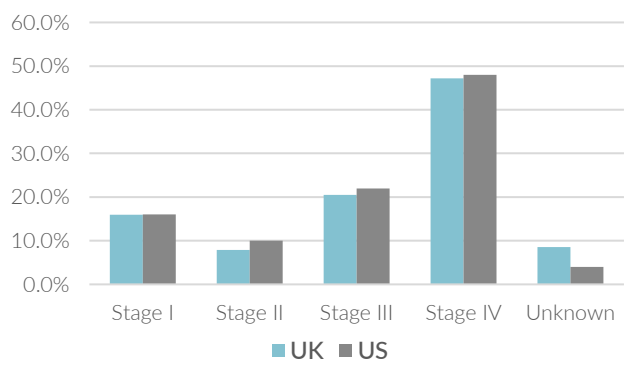
There are three main types of lung cancer, all of which are expected to be detected by Cizzle's variant CIZ1b test:

- **Non-small cell lung cancer (NSCLC):** The most common type of lung cancer comprising about 85% of all cases. NSCLC is itself divided into three subtypes: squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The five-year survival rate differs with the stage at diagnosis, and is ca.60% (localised), 33% (spread to surrounding tissues) and 6% (spread to other organs).
- **Small cell lung cancer (SCLC):** Represents 10%-15% of cases, and characterised by its rapid to spread to other organs, which is reflected in the low five-year survival rates: ca.29% (localised), 15% (surrounding tissues) and 3% (spread).
- **Lung carcinoid tumour (LCT):** Less than 5% of all cases, these tumours are sometimes referred to as lung neuroendocrine tumours, and are characterised by being slow-growing and rarely spreading to other organs. The five-year survival rate is comprised 97% (localised), 87% (surrounding tissues) and 57% (spread).

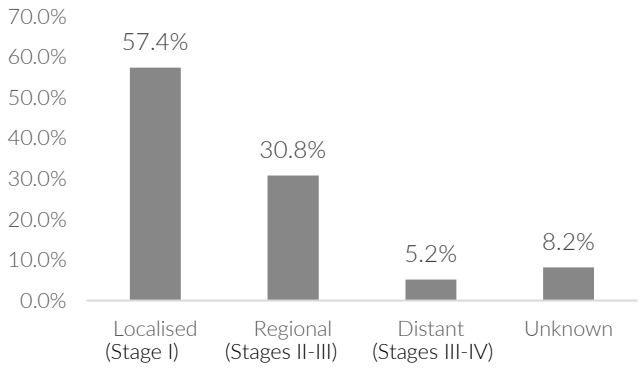
Stage of diagnosis

Data for both the UK[11] and US[12] are broadly similar, with lung cancer patients most commonly diagnosed at stage IV.

Stage of diagnosis and five-year survival rates



Stage at diagnosis



US five-year survival rate

Source: Cancer Research UK, US National Cancer Institute, Hardman & Co Life Sciences Research

[11] Cancer Research UK
[12] US National Cancer Institute

About three quarters of patients are diagnosed at a late stage (72%-76% are diagnosed at stage III or IV), whereas one quarter are diagnosed at an early stage (24%-28% are diagnosed at stage I or II). Therefore, most people are diagnosed at a stage where prognosis is poor, as evidenced by the US five-year survival data.

Presence of lung nodules

Presence of lung nodules does not correlate with presence of lung cancer

Whether through CXT or chest CT scans, one of the first observations to arouse clinical suspicion is the presence of nodules in the lung on the scan. However, this simple observation does not relate directly to the presence of lung cancer. First, the size and growth rate are important; small nodules (<10mm) will probably be ignored. Secondly, in order to assess the growth rate, the clinician will search medical records to see if the patient has had a previous scan; if it is the same size to that seen in previous scans, the nodule is probably unimportant or benign, and will be ignored.

Guidelines[13] from the British Thorax Society provide good advice regarding nodules and provide a clear pathway for patients with nodules. Apart from the clear advice, the report has also assessed the prevalence of nodules on CXR and chest CT scans across different geographical locations, and how many of these cases results in a positive diagnosis of lung cancer. These data are shown in the following table, and indicate that lung nodules will be found in an average of 24% of patients across the world, and that 5.7% of these patients will be identified to have lung cancer.

Prevalence of lung nodules and cancer by geographical location

Geographical area	Studies (n)	Patients (n)	Nodule prevalence Patients		Lung cancer prevalence Patients	
North America	16	83,825	19,280	23%	1,430	1.7%
Europe	13	29,696	8,610	29%	360	1.2%
East Asia	2	24,362	5,100	36%	80	0.5%
Totals	**31**	**137,883**	**32,990**	**24%**	**1,870**	**1.4%**

Source: Adapted from Callister et al., Hardman & Co Life Sciences Research

Prevalence of lung cancer in the US

US statistics for lung cancer are broadly similar to UK statistics

The NCI estimated that there would have been 1.6m patients identified with lung nodules in the US in 2020, and, while many of these will be benign or nothing to do with cancer, 14.3%, or 228,820, new cases of lung cancer would have been found. Lung cancer is the second-most prevalent type of cancer in the US after breast cancer, representing 12.7% of all cancer cases, but is responsible for 22.4% of all cancer deaths (135,720), making it the third-most deadly disease. The late diagnosis of lung cancer is highlighted by the estimated five-year survival rate of just 20.5% in 2019.

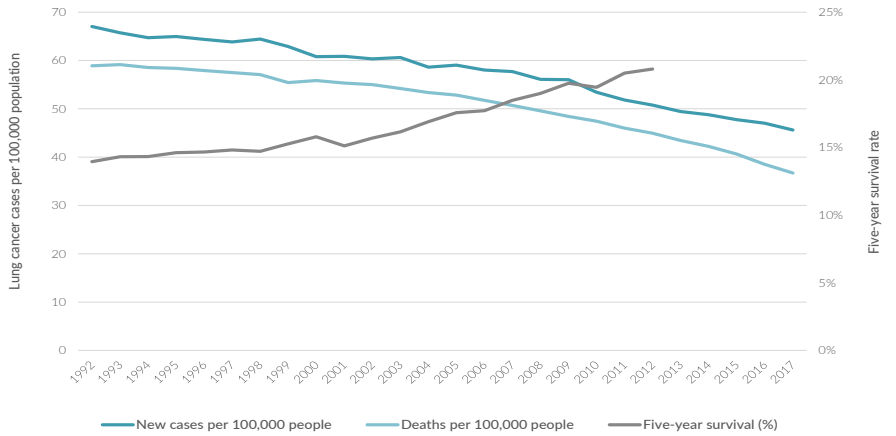
The following graph indicates that there has been a slow, but steady, decrease in the prevalence of lung cancer cases in the US, which has been accompanied by a reduction in deaths. This has seen the five-year survival rate improve from 13.9% in 1992 to 20.5% in 2011, which is probably due to improved screening and modestly earlier detection. However, the NCI itself is indicating that the current five-year survival rate of 20.5% mentioned above is largely unchanged on the 2011 figure.

NCI estimates over half a million people in US living with lung cancer

Cancer.gov suggests that there are an estimated 538,243 people living with lung cancer in the US today[12].

[13] Callister et al., 2015

US lung cancer statistics



Source: www.cancer.gov, *Hardman & Co Life Sciences Research*

Prevalence of lung cancer in the UK

Like the US, there is a staggering quantity of lung cancer patient statistics in the UK. Cancer Research UK states that there were 47,200 new lung cancer cases in 2020, with 75% being at a late stage (III-IV) in people aged 75-89, again highlighting the late diagnosis. It also estimated that there were 35,600 deaths from this disease.

The number of chest CT scans performed in the year to March 2019 was highlighted earlier at ca.566,000. While not all of these will have been ordered because of the presence of previously detected lung nodules (>3cm), many will have been. The large number of false positives will have required up to four follow-up scans over the course of the subsequent two years, draining stretched healthcare resources.

Market potential

At estimated price of £200, the Cizzle test would cost ca.£21m p.a. ...

...but save NHS ca.£83m over two-year period by eliminating unnecessary follow-up scans

Despite coming from a range of sources, the statistics for lung cancer across the world are remarkably similar. Applying those for the UK, the following table sets out the sales potential for a reliable diagnostic biomarker test and also highlights the economic benefit to the healthcare provider through decreased follow-up chest CT scans. On the assumption that the Cizzle test would cost £200 (for example, PSA tests cost £100 and breast genetic/biomarker tests cost £600), the UK market potential is £20.7m p.a. Removing 50% of the false positives from two-year follow-up would result in 207,400 fewer chest CT scans being performed, saving the NHS £83.0m, and generating net savings of £62.3m, over a two-year period.

UK market potential for Cizzle diagnostic	
Number of chest CT scans p.a.	566,000
Those associated with large nodules/high clinical suspicion	24%
Potential lung cancer cases	135,800
Actual lung cancer diagnoses p.a.	47,200
No intervention	32%
Remaining lung cancer patients	32,100
Potential number of false positives	103,700
Estimated cost of test	£200
UK market potential	**£20.7m**
Reduction in those receiving follow-up by 50%	51,850
Potential reduction in chest CT scans over two-year follow-up	-207,400
Cost of chest CT scan	£400
Potential savings to NHS (over two years)	£83.0m
Net potential saving to NHS	**£62.3m**

Source: NHS England, BTS guidelines, Cancer Research UK, Hardman & Co Life Sciences Research

In the US, applying the same calculations, and using a test cost of $400, the sales potential of the Cizzle biomarker would be ca.$115m, and generate potential savings for healthcare providers of ca.$230m over a two-year period.

Competitive landscape

Broad field

Liquid biopsy testing for cancer diagnosis a competitive market place…

…with many technologies

There are a number of different technologies trying to address the cancer diagnostics and monitoring markets. In the same way that Cizzle is uniquely positioned with its variant CIZ1b biomarker for the *in vitro* liquid biopsy market, other companies are uniquely positioned with their technologies (e.g. Oncimmune with its autoantibody technology). Also, there are several players looking at circulating DNA from tumour cells (e.g. Angle) and at tests based on single nucleotide polymorphisms (SNPs) and gene panels.

Potential liquid biopsy competitors to Cizzle

Autoantibody	Biomarkers	Circulating tumour cells	Protein biomarker	Genome-wide sequence variation	SNPs+, gene panels, epigenetics
Not molecular diagnostic	Not molecular diagnostic		Conventional approach	Ultra-deep sequencing	
Oncimmune	Chronix Biomedical Cizzle Biotech Epigenomics	Adaptive Biotech Agena Biosciences* Angle Biocept Cynvenio* EKF Diagnostics Epic Sciences* Vortex	OPKO Health	Grail*	Epigenomics Exosome Diagnostics* Foundation Medicine (Roche) Inivata (NeoGenomics) Oxford Biodynamics Personal Genome Sysmex Inostics

+Single nucleotide polymorphisms
** private company*
This table is unlikely to be comprehensive
Source: Hardman & Co Life Sciences Research

The large equipment and service providers – such as Illumina, LabCorp, Roche and Quest – have not been included in the table as their activities in liquid biopsies and/or specialist tests are very small within their groups' diverse operations. Where these companies come into play is in M&A. Smaller companies are allowed to take all the risk in developing novel tests but are approached when the technology has been substantially de-risked and there is evidence of commercial success. These large players have the financial muscle and operational resources to commercialise the test worldwide.

Lung cancer tests

Key advantage of Cizzle test is its tumour-specific technology

Many blood tests to detect tumour markers are available or under development, but many are hampered by the fact that tumour markers may also be produced by normal cells in the body. In contrast, the Cizzle test uses tumour-specific technology. A number of the tests specific to lung cancer look at particular alterations of circulating DNA (cDNA) and RNA (cRNA) and are used to determine the precise type of cancer, determine which therapy is more likely to work and assess the effectiveness of a particular drug. Few tests are aimed at early detection and reducing significantly the number of false positives achieved via CXR and chest CT scans.

Oncimmune (ONC.L)

Although Oncimmune ahead of Cizzle, it uses a panel system and is targeting more difficult screening market

Oncimmune is a cancer detection company, developing and commercialising its proprietary *Early*CDT platform technology. This platform is based on the presence in the blood of autoantibodies against a panel of specific tumour-associated antigens (TAAs). Oncimmune claims that its tests have the potential to detect cancer up to four years earlier than other methods such as a CXR or a CT scan, and can also be applied to a very wide range of solid tumour types.

Although only £60 per test…

…cost is additive, as not aimed at replacing CT scans

Oncimmune's most advanced, and directly competitive, product is EarlyCDT-Lung aimed at the early detection of lung cancer. EarlyCDT-Lung received CE marking in May 2017 and has been evaluated by NICE[14]. The company claims that EarlyCDT-Lung can detect all type of lung cancer at all stages of disease (I to IV) with high accuracy. It is available at a cost of £600 per test kit, which can run up to 10 samples. However, this is an additional cost as it is not aimed at replacing CT scans.

The company has adopted two commercial strategies:

- **Pulmonary nodule risk assessment:** Positive "rule in" results (as opposed to negative "rule out" results) may help in the assessment of cancer risk in patients with pulmonary nodules, enabling earlier intervention, with a low rate of harm.
- **Lung cancer screening:** This can be used to detect lung cancer early, in high-risk patients. An ongoing NHS clinical trial has demonstrated a stage shift of 55% towards early-stage disease.

Despite extensive validation via a range of large clinical studies, coupled with a wide range of commercial distribution partners across the world, sales of EarlyCDT-Lung, to date, have been disappointing. Despite this, EarlyCDT-Lung must be considered a significant threat, given that it already has CE marking.

Epigenomics (ECXG.DE)

Epigenomics also recognises that the diagnosis of lung cancer remains challenging and represents a highly unmet medical need and that radiological screening methods suffer from a high level of false positives and, therefore, complementary confirmatory diagnostic methods are urgently needed. The company is developing a series of diagnostic tests for various cancers, with Epi proLung specific for lung cancer detection. Epi proLung is based on a combination of proprietary Epigenomics DNA methylation biomarkers SHOX2 and PTGER4. The product received CE marking in Europe in December 2017. Sales to date remain very modest.

Exact Sciences (EXAS)

Exact has proven experience in colorectal cancer, but is only early-stage in lung cancer with a different technology

Exact Sciences (Exact) is a significant competitor because it already has Cologuard regulatory-approved and on the market for non-invasive screening for colorectal cancer. This is a multi-target stool DNA test – including a protein biomarker (hemoglobin), seven distinct DNA point mutation biomarkers (KRAS gene), and two different DNA methylation biomarkers (NDRG4 and BMP3) – which is its distinguishing feature. Therefore, Exact has the experience in developing and commercialising a cancer diagnostic test.

The company is now looking to expand into other cancers, including lung, but these are at an earlier stage of development and its primary focus is currently on liver cancer. However, its collaborators at the Medical University of South Carolina have published an article in Chest[15] showing results with Exact's lung cancer test, which measures the proteins LG3BP and C163A. Given its financial resources, Exact should also be considered a threat to Cizzle.

Comparison of lung cancer diagnostic tests

Characteristic	Cizzle	Epigenomics	Exact Sciences	Oncimmune
Test name	CIZ1b test	Epi proLung		Early-CDT Lung
Biomarker	Variant CIZ1b	SHOX2 and PTGER4	LG3BP and C163A proteins	Circulating tumour cells
Technology	mAb-ELISA	Molecular diagnostic	Molecular diagnostic	ELISA
Identification				Autoantibody
Regulatory position	No approval	CE marking	No approval	CE marking/NICE approval

Source: Hardman & Co Life Sciences Research

[14] National Institute for Health and Clinical Excellence
[15] Silvestri et al., 2018

Financials and investment case

Overview

Annual reports for Cizzle Biotech covering the past eight years are readily available, providing a very good history of financial performance. The company has a track record of spending its limited resources wisely.

Capital increase

Forecasts are based on successful acquisition of Cizzle and £2.2m fund raise…

Concurrent with the acquisition of Cizzle by Bould, the company has raised gross new funds of £2.2m (£1.78m net), primarily to move the test from a WB prototype to a mAb-direct ELISA test ready for CE marking. Further funds would be required for the commercialisation of the test.

Use of proceeds

Target use	Timescale	Cost
mAb generation for CIZ1b and reagent production	9-12 months	£0.08m
Kit development, manufacture and clinical validation	12 months	£0.70m
Health economics and IP	12-18 months	£0.08m
Laboratory services	Next two years	£0.05m
General working capital/contingency	Next two years	£1.00m

Source: Hardman & Co Life Sciences Research

Profit and loss

- **Drivers:** The P&L account will be dominated by the investment in R&D and the corporate overhead during the forecast period. No income is expected, therefore, these costs will drop straight through to the cashflow statement and determine the net cash position at the end of each financial year.
- **Tax credits:** The company is expected to benefit from tax credits on its R&D investment, which is usually received 6-12 months in arrears from HMRC.
- **Acquisition:** The costs of Cizzle's takeover by Bould and the Admission of its shares on the LSE have been treated as an exceptional item.

Balance sheet

- **Net cash:** The Admission document states that the *pro forma* financial position of the enlarged entity will be £1.78m, following the Placing to raise gross new capital of £2.2m.
- **Assets:** Other than its IP, the enlarged entity does not have any other assets.

Cashflow

…giving cash runway of 18-24 months

- **Capital increase:** Funds raised at the time of the acquisition will fund the R&D investment and general working capital requirement over the forecast period.
- **Costs:** We have assumed that the professional fees associated with the acquisition and Admission will be in the order of £810k, which is shown as an exceptional item in the cashflow statement. The net funds after all costs associated with acquisition and Admission of the shares, to support future operations, are stated at £1.78m.
- **Cash runway:** The target fund raise is expected to provide a cash runway of approximately 18-24 months. The company will need to raise further capital before the end of fiscal 2022.

History and forecasts

Financial summary						
Year-end Dec (£000)	2017	2018	2019	2020E	2021E	2022E
Profit & Loss						
Sales	0	0	0	0	0	0
COGS	-74	0	0	0	0	0
SG&A	-68	-54	-22	-15	-300	-500
Share-based costs	0	0	0	0	-20	-50
R&D	0	0	0	0	-250	-500
Licensing/royalties	2	51	0	0	0	0
Underlying EBIT	**-140**	**-3**	**-22**	**-15**	**-570**	**-1,050**
Exceptional items	0	0	0	0	-810	0
Statutory EBIT	-140	-3	-22	-15	-1,380	-1,050
Net financials	0	0	0	0	0	0
Underlying PBT	**-140**	**-3**	**-22**	**-15**	**-570**	**-1,050**
Statutory PBT	22	0	0	0	50	100
Tax liability/credit	22	0	0	0	50	100
Underlying net income	-118	-3	-22	-15	-520	-950
Underlying basic EPS (p)	**-37.6**	**-0.9**	**-6.9**	**-4.8**	**-0.3**	**-0.4**
Statutory basic EPS (p)	-37.6	-0.9	-6.9	-4.8	-0.8	-0.4
Balance sheet						
Share capital	3	3	3	3	26	26
Reserves	28	25	3	-12	1,646	696
Leases	0	0	0	0	0	0
Loans & borrowings	0	0	0	0	0	0
less: Cash & deposits	13	20	13	0	1,290	425
Invested capital	**18**	**8**	**-6**	**-8**	**382**	**297**
Cashflow						
Underlying EBIT	-140	-3	-22	-15	-570	-1,050
Change in working capital	-35	8	15	2	100	85
Company op cashflow	**-172**	**7**	**-7**	**-13**	**-450**	**-915**
Capital expenditure	0	0	0	0	0	0
Equity issues	0	0	0	0	2,200	0
Change in net cash/(debt)	**-150**	**7**	**-7**	**-13**	**1,290**	**-865**
Opening net cash/(debt)	171	13	20	13	0	1,290
Closing net cash/(debt)	**13**	**20**	**13**	**0**	**1,290**	**425**

Source: Hardman & Co Life Sciences Research

Valuation

Valuing private companies with relatively limited financial information and forecasting can be quite difficult; therefore, we use a multi-disciplinary approach to provide readers with as much information as possible in order for potential investors to make an informed judgement about whether the combined Bould/Cizzle entity is a good investment opportunity.

DCF analysis

In our opinion, the best approach to valuing biotech companies is to prepare detailed discounted cashflow (DCF) analyses of key products and/or technologies through to patent expiry and then to risk-adjust the NPV, based upon industry standards for the probability of the product reaching the market. However, in order for this to be successful, there needs to be a long period of forecasts, based on actual data derived from historical benchmarks. In this instance, the assets are still in the development phase, and there is only a modest level of benchmark information available regarding liquid biopsies. In addition, it is difficult to predict what will happen when the patents expire and given the likelihood that there will be a terminal value.

Despite these reservations, we have performed a DCF analysis, using the performance of Cologuard (Exact) as precedent for test use when it becomes available commercially. In addition, we have used the following key assumptions:

- **Price:** As indicated earlier in this report, we have used £200 for the UK market and $400 for the US market.
- **Launch:** Further development of the test through to CE marking is likely to take two years, with potential launch in 2025 in the UK; for the US market, we have assumed that the test will be available as a Laboratory Developed Test (LDT) in the first instance, from 2027.
- **Margin:** In the UK, provided that Cizzle can get the test onto the appropriate "Lung Cancer Pathway" guidelines, thereby reducing marketing costs, the margin is likely to be relatively high, at 65%. In the US, the need for a laboratory partner would reduce this to an estimated 40%.
- **Development risk:** To allow for the fact that several things need to be done to move from a prototype test to a regulatory approved commercial test, a risk factor of 67% has been applied to the NPV (i.e. a 33% chance of a successful outcome).

DCF generates valuation of £21.7m, based on the UK and US opportunities alone

Although not a core assumption, our DCF model had been applied only to the UK (home market) and the US (important diagnostics market), primarily because of the extensive statistics on scans and lung cancer that are available to us. Therefore, the model is conservative, as highlighted by Professor Harry DeKoning at an international conference on screening and early detection of lung cancer (Barcelona, October 2019), who stated that there would be a big push for improving diagnosis in Europe from 2020. Moreover, there is an enormous increase in the demand for diagnostics in SE Asia, particularly in China. However, any push by Cizzle into these markets would require further R&D and an increase in working capital.

Therefore, based on the core assumptions listed above, the risk-adjusted value of the Cizzle technology platform is £21.7m.

Summary of DCF analysis			
WACC	NPV ($m)	NPV (£m)	Risk-adjusted NPV (£m)
8%	101.9	81.5	26.9
9%	91.4	73.1	24.1
10%	**82.1**	**65.7**	**21.7**
11%	73.9	59.1	19.5
12%	66.7	53.3	17.6

Source: Hardman & Co Life Sciences Research

Comparative valuation

An alternative approach to valuation is to undertake a peer group comparison, whereby the value of Bould/Cizzle can be put into context against the stock market valuations afforded to a group of similar companies. However, while this is a sound approach to take, in practice it is much less straightforward, for a number of reasons:

- companies are all using slightly different technologies and approaches;
- even using the same approach, different targets/indications are being tackled;
- currently, UK biotechs are being unduly negatively influenced by certain market forces; and
- irrespective of the above point, it is well-known that the UK stock market affords lower valuations to companies compared with similar companies quoted on other stock markets, notably NASDAQ.

Comparative valuations suggest that Cizzle would be trading at a 78% discount…

…reflecting early stage of development

The companies detailed below are close peers of Cizzle, all working in the field of specialist diagnostics/liquid biopsies, mostly in the field of oncology. It should be noted that the share prices of these companies have been extremely buoyant over the past 12 months because they have been able to adapt their test technology to be used for COVID-19 (SARS-CoV-2) tests. In addition, while Angle is not involved in tests for COVID-19, its share price has been strong, as its cancer tests approach regulatory approvals and commercialisation.

- The average EV of UK diagnostic peers is £109.2m (range £39.8m-£211.2m).
- The relative EV of UK peers to the valuation of Cizzle at the time of Admission is in the range 1.6x to 8.7x, with an average of 5.3x.
- The enlarged Cizzle/Bould entity at the time of Admission will have an EV of £24.4m. This suggests that the company would be trading at a 78% discount to its peer group average, reflecting the fact that its technology is at an earlier stage of development. This suggests that there is considerable upside potential on positive news about development of its test in the future.

UK peer group valuations

Company Ticker	Angle AGL	Cizzle CIZ	Genedrive GDR	Omega Diag. ODX	Oncimmune ONC
Share price	110.0	10.0	67.0	68.0	218.0
Shares in issue (m)	215.7	261.1	63.3	182.6	69.1
Market cap. (£m)	237.2	26.1	42.4	124.2	150.7
Cash (£m)	26.0	1.7	2.8	5.7	10.0
Debt (£m)	0.0	0.0	-0.2	-1.0	-10.5
EV (£m)	**211.2**	**24.4**	**39.8**	**119.5**	**151.2**
Relative EV (x)	8.7	-	1.6	4.9	6.2

Share prices taken at close of business on 12 May 2021
Source: Hardman & Co Life Sciences Research

Combined entity

The combined, enlarged entity would have market capitalisation of £26.1m

On completion of the acquisition, the market capitalisation of the enlarged entity should reflect the fair value of Cizzle, the value ascribed to Bould, plus the net cash within the combined entity after taking account of the costs of the listing and fundraise, giving a total market capitalisation of £26.1m.

Company matters

Registration

Bould Opportunities is incorporated in England and Wales with company registration number 06133765.

Cizzle Biotechnology Limited is incorporated in England and Wales with company registration number 5249093.

Registered office:

80 Cheapside

London

EC2V 6EE

Board of Directors

Completion of the acquisition and readmission of its shares on the London Stock Exchange Main Market has triggered changes to the board of directors.

Board of Directors on Admission			
Position	**Name**	**Remuneration**	**Audit**
Executive Chair	Allan Syms		
Finance Director	Nigel Lee		
Non-executive director and founder of Cizzle	Dawn Coverley		
Non-executive director	John Treacy	C	C

C = chair

Source: Company reports

Allan Syms – Executive Chair

Allan is an experienced public and private company director, with a background in Corporate Finance, IPOs and managing strategic change. Allan holds a PhD in cancer research and began his corporate career at GE Healthcare (formerly Amersham International PLC). He has spent the past 30 years creating and, through private and public fundraising, building emerging technology businesses. He was previously an adviser to the Department of International Trade.

Prof. Dawn Coverley – Non-Executive Director, Founder of Cizzle

Dawn Coverley is a cell biologist with 20 years' experience in basic cancer-related research. After a first degree in Genetics (University of Leicester) and a PhD in biochemistry (Cancer Research UK), she moved to Cambridge University in 1992. Her research exploits experimental systems that reconstitute fundamental processes associated with DNA metabolism, including DNA repair and DNA replication, and she has generated original research articles published in peer review journals including Nature and Nature Cell Biology. In 2001, she was awarded a senior research fellowship by the Lister Institute of Preventive Medicine and established a new research laboratory at the University of York. She founded Cizzle Biotech in 2005, and raised seed corn funding in 2006. She is currently principal investigator of an academic DNA replication research laboratory at York and, following the acquisition of Cizzle, will be a scientific advisor and sit on the Board as an NED.

Nigel Lee – Finance Director

Nigel qualified as an accountant in 1988 and spent 11 years at PricewaterhouseCoopers (PwC), gaining audit and business advisory experience. In the period 1999-2003, he was finance director or finance controller at a number of IT services and software companies. Nigel has considerable audit and business advisory experience developed from clients encompassing unquoted through to multi-national companies, including a number of pension funds. He will join Cizzle as Finance Director on Admission.

John Treacy – Non-Executive Director

John is a London-based experienced small-cap financier who specialises in working with growing companies. He qualified as a solicitor in the London office of a major international law firm where he specialised in Capital Markets and M&A. From there, he moved to practise corporate finance in the advisory teams of several prominent UK brokerages, where he acted as an adviser to a number of companies and advised on numerous IPOs, acquisitions, debt restructurings and placings.

Advisors

Professional advisors

Role	Advisor
Financial Advisor	Allenby Capital Ltd
Corporate Broker	Novum Securities Ltd
Legal Advisers	Goodman Derrick LLP Shakespeare Martineau LLP
Auditors	PKF Littlejohn LLP
Financial Public Relations	IFC Advisory Ltd
Registrar	Link Group

Source: Company reports, Hardman & Co Life Sciences Research

Share capital

Prior to the changes, Bould Opportunities plc had 12,408,442,268 Ordinary shares of 0.01p nominal value in issue. At the point of completion, Bould undertook a 500-for-1 share consolidation.

Cizzle Biotechnology Ltd had 313,932 Ordinary shares in issue. Under the acquisition agreement, existing shareholders will receive their respective proportion of 206,310,904 new consideration Ordinary shares in Bould for each existing share held.

Concomitantly, Bould has issued 22.0m new Ordinary shares @10p per share to raise gross new capital of £2.2m for R&D investment and working capital purposes, as indicated earlier.

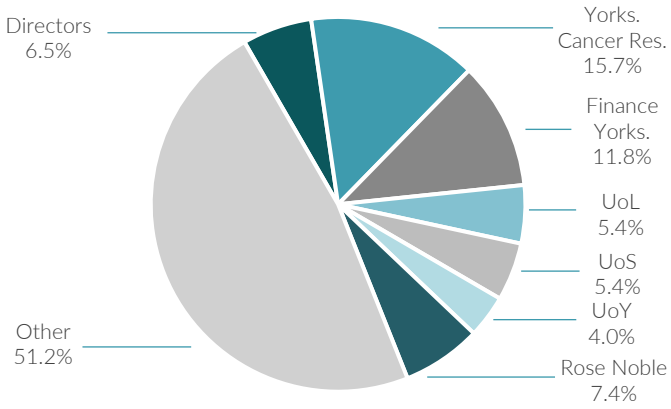
Following all these transactions, there will be 261,051,150 Ordinary shares in issue, and the company will be renamed Cizzle Biotechnology Holdings plc.

Share analysis on Admission

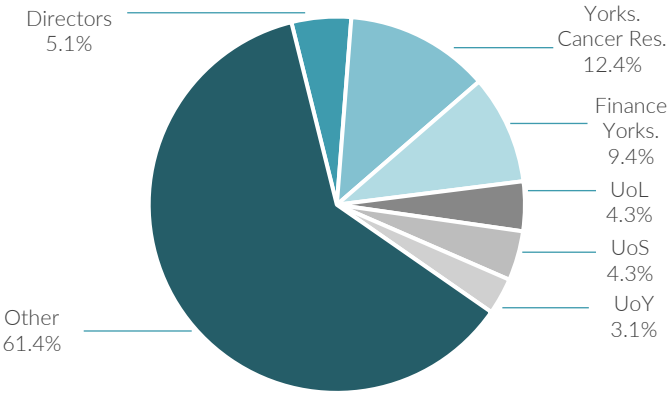
	Number of shares
Shares of Bould Opportunities after consolidation	24,816,815
Consideration shares to Cizzle shareholders	206,310,904
Antos option shares	7,603,432
Peterhouse shares	320,000
Fundraise shares concomitant with Admission	22,000,000
New enlarged capital	**261,051,150**

Source: Admission document, Hardman & Co Life Sciences Research

Shareholders



Cizzle Biotech alone



Enlarged entity

Source: Admission document, Hardman & Co Life Sciences Research

Risks

It goes without saying that investments in small, early-stage companies carry a significant risk, and investors must be aware of this fact.

In our opinion, the following risks are particularly relevant.

Stage of development

While Cizzle has proof-of-principle of its variant CIZ1b test using WB, this is not suitable for high-throughput laboratories and commercialisation. The company needs to develop an ELISA test using a monoclonal antibody. Development of such an antibody can take 9-12 months. Following this, the next-generation test will need validation.

Patent robustness

As with all medtech and diagnostic products, there is risk that the IP is insufficiently covered by global patents.

Regulatory approval

Cizzle is operating in a field potentially subject to tight and changing regulation. Although its product could potentially be launched in the US as an LDT without formal regulatory approval, having FDA (via a PMA or 510(k)) and EU (via CE marking) regulatory approval confers considerable advantages and a certain level of market protection. Such regulatory processes are time-consuming and need to be supported, generally, by potentially expensive clinical trials.

Competition

Although the technology approach being taken by Cizzle is unique, with few researching CIZ1 globally, other technologies can be used to obtain similar outcomes, all with the aim of improving clinical decisions. The competition section (pages 20-21) highlights the large number of companies developing and/or commercialising diagnostic tests and this ignores the large specialist clinical laboratory groups that control much of the market.

Commercialisation and pricing

Although the commercialisation strategy is yet to be finalised, Cizzle will be helped by the fact that some competitor liquid biopsy biomarker products have been priced and are being reimbursed by payers in both Europe and the US at levels that will provide an adequate return. Strong pharmaco-economic data are required in order to obtain these pricing structures. However, as more products enter the market, it is conceivable that prices might come under some pressure.

Dilution risk

Our forecasts suggest that the current funding will be sufficient to reach particular milestones, notably submission for CE marking. However, in order to enact its commercialisation strategy, and to develop other tests, further funding will be required. Shareholders could suffer significant dilution if they do not participate in further funding rounds.

Share liquidity

An investment in the company might not be suitable for all recipients of this publication. Market liquidity is very poor at present, making it potentially difficult for investors to sell their shares.

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Glossary

510(k)	Pre-market submission made to the FDA to demonstrate that a medical device to be marketed in the US is at least as safe and effective, that is, substantially equivalent, to a currently legally marketed device.
CE	Conformité Européenne marking, a mandatory European health and safety product label used on many products in the European Economic Area. CE marking certifies that a product has met EU consumer safety, health or environmental requirements.
CIZ1	Cdkn1A-interacting zinc finger protein 1
CRO	Contract research organisation
CT	Computerised tomography
CXR	Chest X-ray
DCF	Discounted cash flow
DNA	Deoxyribonucleic acid, the carrier of genetic information
ELISA	Enzyme-linked immunosorbent assay. Development of the ELISA was based on the observation that antibodies or antigens can be adsorbed to a solid surface and still participate in high-affinity binding. The term ELISA now refers to a wide range of immunoassays some of which do not involve enzymatic reactions. However, the commonality among all ELISAs is the use of antibodies, which play a major role in determining the sensitivity and specificity of the assay.
FDA	US Food & Drug Administration
LCT	Lung carcinoid tumour
LDT	Laboratory developed test
mAb	Monoclonal antibody
NCI	The US National Cancer Institute
NHS	The National Health Service of the UK
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
TAA	Tumour-associated antigen
WB	Western blot – an analytical technique which is used to pinpoint a specific protein in a given sample. It exploits the ability of an enzyme or fluorescence-labelled primary antibody to bind to its specific antigen. Although it has high sensitivity and specificity it can still produce erroneous results when the antibody reacts with a non-target protein. It also requires high levels of analytical quality control and is technically demanding, making it unsuitable for large-scale screening.

Notes

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research@hardmanandco.com

1 Frederick's Place
London
EC2R 8AE

+44 20 3693 7075

www.hardmanandco.com