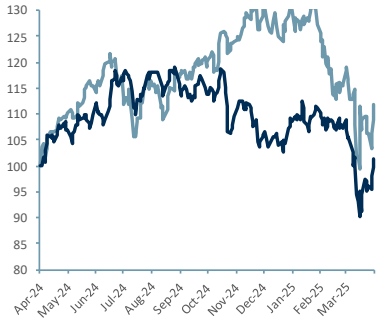
THEMATIC RESEARCH ONCOLOGY

Lung Cancer Cough (LCC) US Market

An Introduction to Value of the US LCC Market



Price relative Nasdaq Comp (lighter line) vs. Nasdaq Biotech

Friday, 25 April 2025

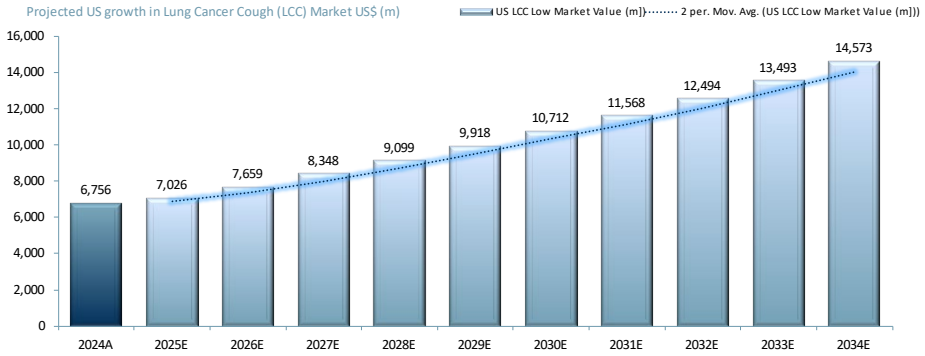
Thematic Sector
Biotechnology & Medical Research

Public Companies in Note	**% from 52 wk high**
Merck & Co	41.5%
Teva Pharmaceuticals	37.3%
Merus N.V.	32.1%
Pfizer	29.0%
AstraZeneca	21.9%
GlaxoSmithKline	19.4%
Eli Lilly	14.7%
Summit Therapeutics	10.0%
Novartis	8.9%
Enterprise Value (EV)	**US$ bn**
Merck & Co	224.8
Teva Pharmaceuticals	31.6
Merus N.V.	2.8
Pfizer	191.8
AstraZeneca	455.9
GlaxoSmithKline	70.5
Eli Lilly	845.4
Summit Therapeutics	27.0
Novartis	239.4

Healthcare Sector Research
NASDAQ Market Index
ACF Healthcare Team
+44 20 7419 7928
healthcare@acfequityresearch.com

Lung Cancer Cough (LCC) is an under-served, perhaps unserved therapeutic subsegment of the Lung Cancer/Oncology market. 57-65% of early diagnosis lung cancer patients suffer from LCC, it is a highly debilitating condition. The US lung cancer therapeutics market consensus values range from ~USD 29.9bn in 2023 to ~USD 71.3bn in 2034, suggesting a compound annual growth rate (CAGR) of 8.2% over our 10 year forecast period. LCC is a prevalent symptom among lung cancer patients, and its management is integral to patient care, however the mechanism of LCC is little researched and poorly understood. By this we mean that it is uncertain in a significant proportion of cases as to the underlying cause of the LCC symptoms. As such we assume a competitive market even for a therapy with 'knockout' therapeutic benefits or improvements.

- Lung Cancer incidences in US, cohort 234,580 people p.a.;
- LCC sufferers 57-65% of early diagnosis US LC incidences;
- Market pharmacologically 70% of US LCC sufferers;
- Pharmacological NPV market value for US LCC ~USD 1bn+;
- Quality of life market ~80% of late stage US LC sufferers.



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Investment Case

The United States LCC market has an NPV of USD 1bn+ assuming a FCF margin of 20% and a WACC of 20% in our forecasts. Consensus forecasts suggest a more valuable market. LCC US therapeutic estimates are made difficult to isolate because the limited number of therapies available tend to have LCC as a secondary indication, which means they are administered for LC but appear to have some positive effects on LCC. In essence, there is currently no decisive cure or palliative.

Whilst specific, reliable, data isolating the current market value for treatments addressing lung cancer cough (LCC) in lung cancer patients is more or less non-existent, using investment research analytical, statistical techniques, read-through and meta-analysis approaches, we can generate LCC value ranges with rational assumptions within the broader lung cancer therapeutics market. Whilst this means the market will appear to be competitive, at least initially, for a transformative new therapy, it equally means a transformative therapy could, 2-3 years after launch, dominate the market.

LCC is a prevalent symptom among lung cancer patients, and its management is integral to patient care, it should be noted that one of the challenges of penetrating the LCC market with a therapy is that the mechanism of LCC is little researched and poorly understood. By this we mean that it is uncertain in a significant proportion of cases if the LCC symptoms are caused by lung cancer or have some other underlying cause.

In our view, this 'uncertain mechanism' adds an additional element of difficulty or risk for healthcare companies when it comes to assessing the level of efficacy of proposed therapies during trials and during marketing. This in turn crystallizes in valuation as an additional risk to potential market penetration rates and peak penetration if an LCC therapy delivers only a marginal improvement.

Our US only market value ranges for LCC treatments is determined by factors including the prevalence of lung cancer, the percentage of patients experiencing LCC, the availability and adoption of therapeutic options, and the cost associated with these treatments. We have taken a consistently highly conservative approach to assessing the value of this market, in part because of the lack of robust or indeed any consensus market forecasts for US or global LCC value.

Investment Strategies

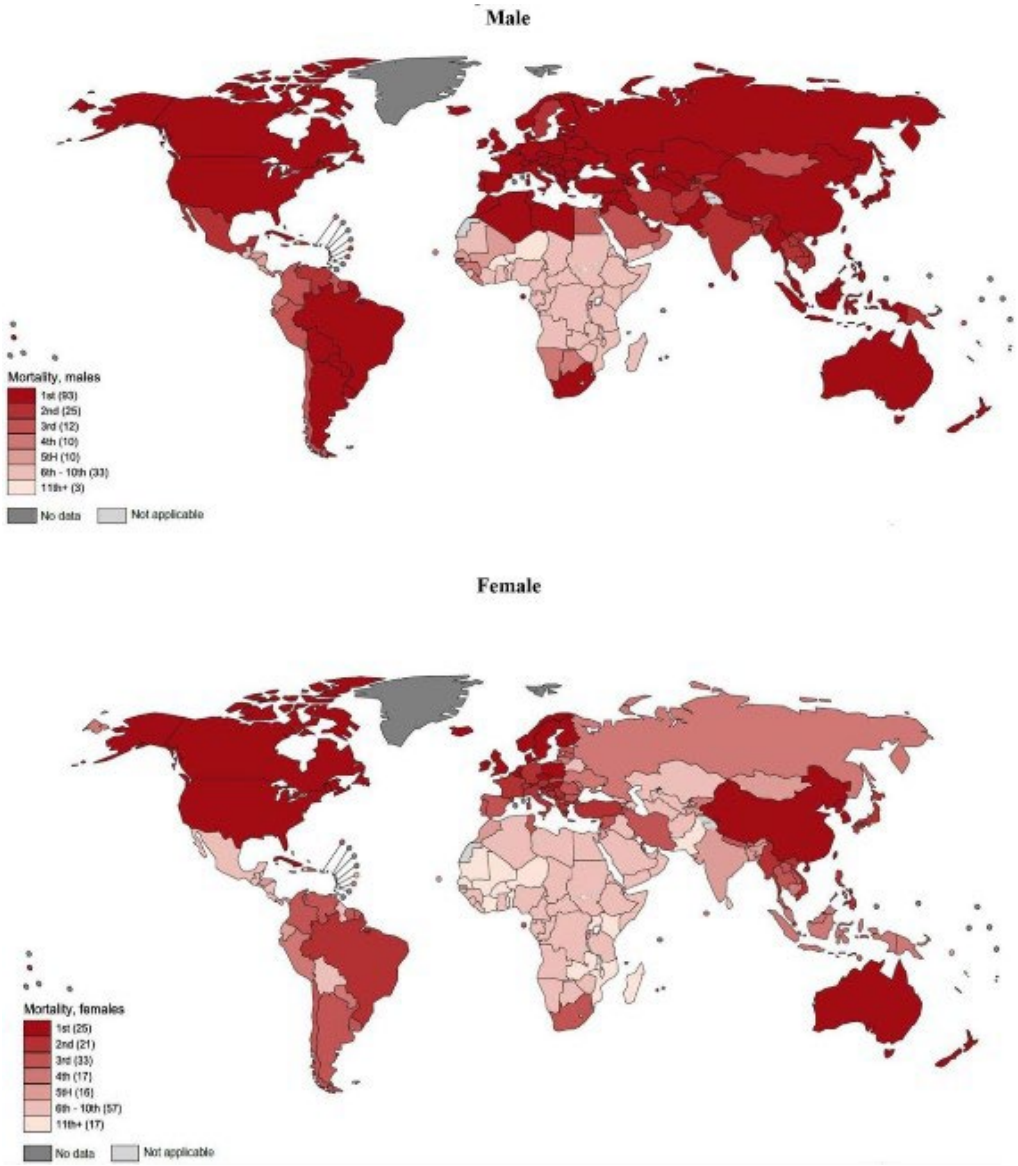
1. Growth-Oriented Approach - Focus on companies with strong pipelines and low capex **2.** Diversification - Combine large caps e.g., Novo Nordisk with investigational pre-revenue stocks and private companies e.g., Biovara Limited. **3.** Thematic ETFs - e.g., iShares Biotechnology ETF (IBB) for diversified indirect exposure to LCC innovations.

Lung Cancer Cough Biochemistry – An Introduction

Exhibit 1: **Lung cancer by country 2020 estimates**

The maps in the exhibit serve as a proxy for the incidence concentration of lung cancer cough (LCC), which whilst affecting around 60% of all lung cancer sufferers can rise to 80% in the final stages of lung cancer disease progression.

The exhibit maps indicate lung cancer's position in terms of deaths relative to other common tumours at the national level, by sex for the year 2020. In 2020, lung cancer was the leading cause of cancer death in half (93 out of 185) of the countries included in GLOBOCAN, and either second or third in a further 37 countries, in men. Women suffer lower mortality rates than men however it is nevertheless significant and lung cancer is the leading cause of cancer related mortality in 54 of 185 countries globally in women.



Sources: BMJ Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020

The biochemistry and pathophysiology of lung cancer-related cough (LCC) is very poorly understood and is a complex interplay of tumour biology, neural pathways, inflammatory mediators, and mechanical factors.

Exhibit 2: **Possible pathway to Lung Cancer Cough**

Tumour → Airway Irritation + Inflammation → Cytokines+Prostaglandins+Bradykinin → Vagus Nerve & C-fibre Sensitization → Lowered Cough Threshold → Chronic Cough

Sources: ACF Equity Research

Cytokines are small proteins that act as signalling molecules essential to the immune system response. Cytokines are implicated in immune responses including inflammation regulation and blood cell production. Types of Cytokines include:

Chemokines – Direct immune cells to sites of infection or injury.

Interferons – Viral cell defence.

Interleukins - Communicate between white blood cells to coordinate immune responses.

Tumour Necrosis Factors (TNFs) - Inflammation regulation, can help kill tumour cells.

Colony-Stimulating Factors (CSFs) - Stimulate the production of blood cells.

Prostaglandins are hormone-like lipid compounds, derived from arachidonic acid, They play pivotal roles in various physiological processes including inflammatory responses.

Bradykinin is a peptide that impacts blood pressure regulations and inflammation by causing blood vessels to dilate (widen) and increasing the permeability of capillaries, permitting fluid diffusion into other tissues.

The vagus nerve (the 10th cranial nerve (CN X)), is the longest cranial nerve in the body. It runs from the brainstem all the way down to the abdomen starting in the medulla oblongata, running down the neck between the carotid artery and the jugular vein, through the chest influencing heart and lung function and terminates in the abdomen where it effects changes in the digestive tract.

1. Peripheral Sensitization – Airway Receptors - **Tumour-induced airway irritation** from lung tumours invades or compresses airways, this in turn stimulates cough receptors (mechanoreceptors and chemoreceptors) in the respiratory tract. In addition, **C-fibre activation** - C-fibres are unmyelinated sensory neurons sensitive to chemical and mechanical stimuli. Tumours and associated inflammation release irritants that activate these fibres. **Mucus production and obstruction** - Tumours can obstruct airways, leading to mucus accumulation. The body attempts to clear mucus via coughing, irrespective of whether the cough is productive or non-productive.

2. Neural Pathway Dysregulation - Vagal nerve involvement - The vagus nerve is a central element of the cough reflex arc. Lung tumours can irritate or compress branches of the vagus nerve, triggering and or exaggerating the cough reflex.

3. Inflammatory Mediators & Cytokines - **Pro-inflammatory cytokines** (e.g., IL-1β, TNF-α, IL-6) are elevated in lung cancer. These cytokines can sensitize cough receptors, also inflammatory mediators including **prostaglandins and bradykinin** are indicated in sensitizing airway nerves. These factors mean that patients are more likely to cough, and for longer periods of time.

4. Neurokinin Pathways - **Substance P and Neurokinin A**, neuropeptides involved in neurogenic inflammation, are upregulated in lung cancer and may add to cough hypersensitivity.

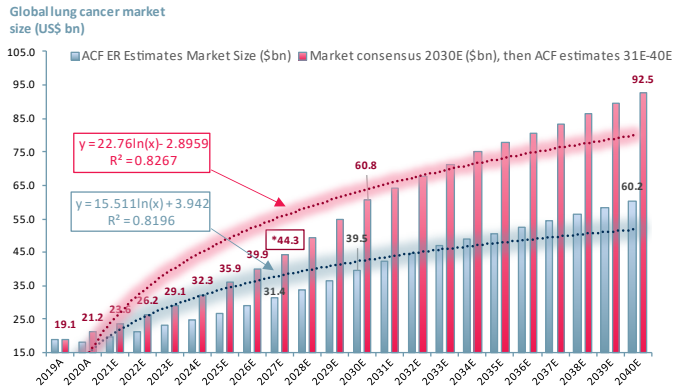
5. Tumour-Derived Factors - Ectopic hormone/peptide secretion - Small cell lung carcinoma in particular, causes the secretion of hormones or peptides (e.g., ACTH, serotonin) that are thought to have potential to influence cough reflexes indirectly.

6. Oxidative Stress - Lung tumours create a pro-oxidative environment, producing reactive oxygen species (ROS). These ROS can activate cough receptors and damage airway epithelium, enhancing cough reflex sensitivity.

7. Central Nervous System Sensitization (fewer studies) - There is limited research on persistent coughing that may then possibly lead to central nervous system changes (viz chronic pain).

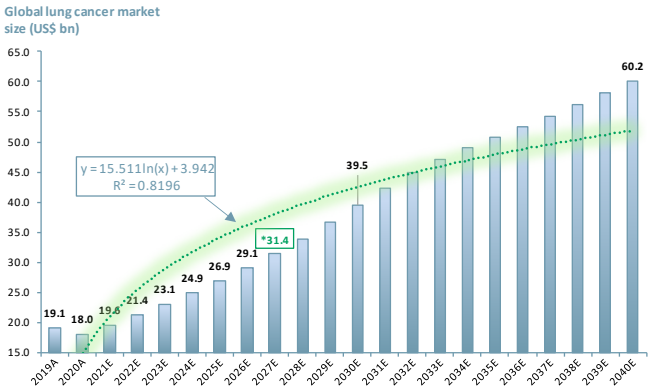
Lung Cancer Global Prevalence

Exhibit 3: Consensus Global LC Market



Sources: ACF Estimates, ACF Graphics, Fortune Business, BCC Research, Acumen. Market Research Future.

Exhibit 4: ACF Global LC Market



Sources: ACF Estimates, ACF Graphics.

Lung Cancer Market Therapeutic Value Forecasts - Whilst the lung cancer market therapeutic value is forecast to grow to 2040, the supportive care drugs market, the segment in which LCC therapies and palliatives are currently classified, is projected to decline with a CAGR of -1.26% to 2030 (source Grand View Research). Nevertheless, LCC therapies as part of the supportive care drugs market, if currently in decline, are most likely suffering from an inability to link efficacy directly to reduced LCC.

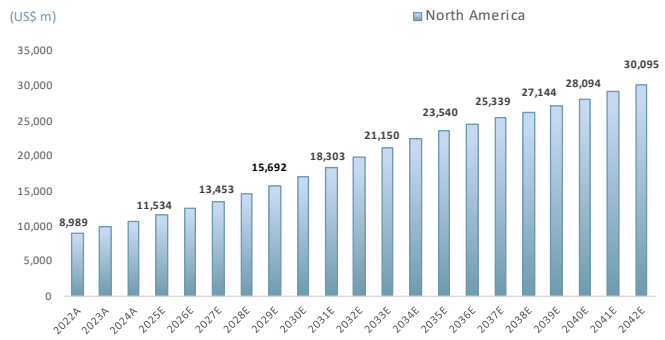
Prevalence of Lung Cancer Cough (LCC) Among Lung Cancer Patients – LCC is a common symptom among lung cancer patients. Studies provide evidence that LCC is present in between 57% and 65% of patients at the time of lung cancer diagnosis and that this progresses to 80% in late stage lung cancer patients.

Demographic Factors: Age and Sex - **Age:** Lung cancer primarily affects older adults. The average age at diagnosis is approximately 70 years, with most cases occurring in individuals aged 65 or older. **Sex:** Historically, men have had higher rates of lung cancer compared to women. However, the gap has been narrowing in recent years.

Regarding the prevalence of LCC among lung cancer patients, studies have not found significant associations between LCC prevalence and demographic factors such as age and sex. For instance, a cross-sectional study concluded that age and sex were not associated with LCC prevalence among lung cancer patients.

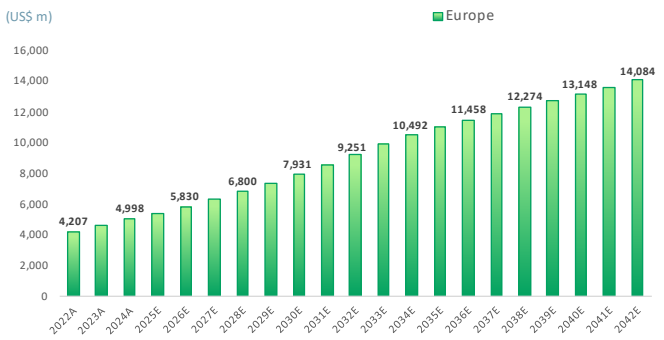
Lung Cancer United States Prevalence

Exhibit 5: 'US' LC Market [ACF Est.]



Sources: ACF Estimates, ACF Graphics.

Exhibit 6: Europe LC Market [ACF Est.]



Sources: ACF Estimates, ACF Graphics.

According to the American Cancer Society, approximately 234,580 new cases of lung cancer are expected in the United States in 2024 (once the data is collated), representing a marginally declining trend since 2021, with a demographic split of ~116k cases in men and 118k cases in women, suggesting a minor predominance in women. This declining overall trend is attributed to factors such as reduced smoking rates and advancements in early detection and treatment. However, an aging population trend may offset these declines to some extent, and more importantly in our view, environmental factors related to air quality and the enormous uptake of vaping et al may serve to gently accelerate incidence growth rates in the future. Lung cancer currently predominantly affects older individuals (vaping conceivably could change this demographic character).

Therefore, a rational modelling approach in our assessment could lead to projections describing a slight decrease to a stabilization in the number of new cases over our 10 year projection period. For this thematic research we have opted for a stable number of cases per annum.

Projections for Lung Cancer Cases - Market consensus forecasts for the number of lung cancer cases over the next decade are notably variable. Irrespective of our insights, investors should note that trend analysis is suggesting the beginnings of a gradual decline in lung cancer incidence rates.

Lung cancer remains a significant health concern in the United States, with a substantial number of new cases diagnosed annually. LCC is a prevalent symptom among these patients, affecting 57-65%, at the time of diagnosis. While lung cancer predominantly affects older adults, the incidence between men and women has become more comparable in recent years. Notably, the prevalence of LCC does not appear to be significantly influenced by age or sex demographics.

Lung Cancer Cough US Therapy Market Forecasts

Our inference is that the US lung cancer cough market represents a meaningful USD value component of the overall lung cancer therapeutics landscape. In our first pass assessment there are reasonable and rational reasons to infer that there exists a substantial opportunity for investment and development in effective LCC management solutions for enhanced patient outcomes and meaningfully improved quality of life.

Current Market Value and Determination for Lung Cancer Cough (LCC) - Whilst specific and or reliable data isolating the current market value for treatments addressing lung cancer cough in lung cancer patients is more or less non-existent, using investment research analytical and statistical techniques, we can infer its significance and generate value ranges with certain rational assumptions within the broader lung cancer therapeutics market.

LCC is a prevalent symptom among lung cancer patients, and its management is integral to patient care. It should be noted that one of the challenges of penetrating the LCC market with a therapy is that the mechanism of LCC is little researched and poorly understood. By this we mean that it is uncertain in a significant proportion of cases as to whether the LCC symptoms are caused by lung cancer or have some other underlying cause.

In our view, this 'uncertain mechanism' adds an additional element of difficulty or risk for healthcare companies when it comes to assessing the level of efficacy of proposed therapies during trials and during marketing. For a therapy that delivers only a marginal improvement, we assess there is a negative valuation impact expressed via lower and or slower market penetration rates and time to peak penetration assumptions.

In line with the reasoning summarized above we have a particularly conservative potential NPV contribution in our low case scenario.

Our value range for LCC treatments is determined by factors including the prevalence of lung cancer, the percentage of patients experiencing LCC, the availability and adoption of therapeutic options, and the cost associated with these treatments.

Cost estimate of LCC Treatment on a monthly basis is used to infer potential new LCC therapy pricing. The cost of managing LCC in lung cancer patients varies based on the treatment modality:

Medications - Prescription medications aimed at suppressing LCC can cost over $4,000 pcm.

Radiation Therapy - Employed in certain cases to reduce tumour size and alleviate LCC, can exceed $9,000 pcm (though we assume this would be for a particularly limited time period).

Supportive Care - Palliative measures, including supportive care without aggressive treatments, can average around $3,000 pcm.

It is important for investors to note that these figures can vary based on insurance coverage, geographic location, and individual patient needs.

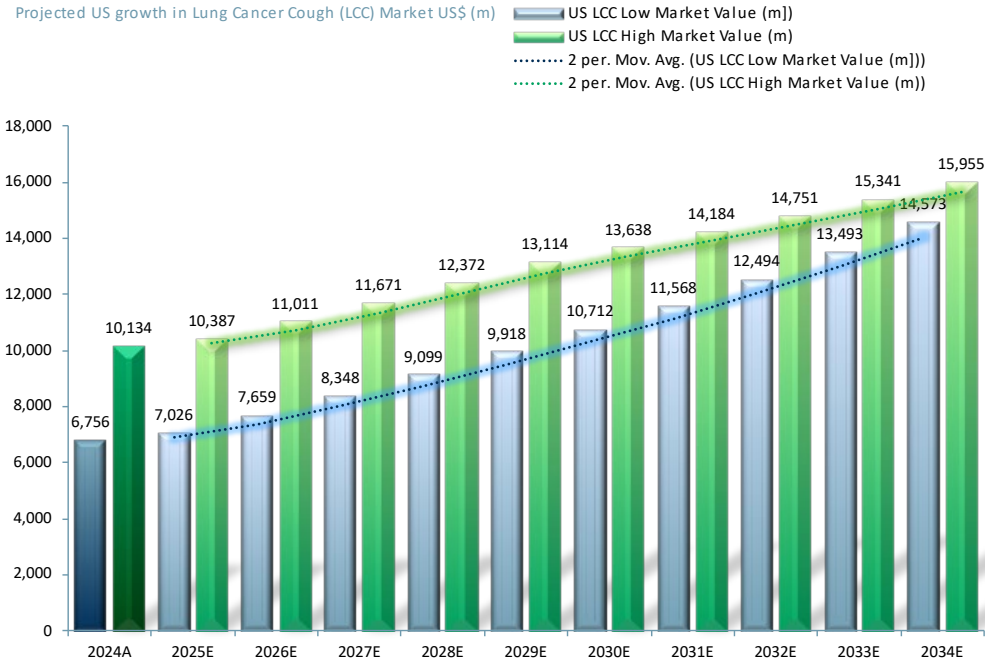
Projected LCC Market Value in 10 Years 2025-2034E USD 7.0-15.9bn, CAGR 7.99%- Considering our overall growth trajectory consensus led assumptions for the US lung cancer therapeutics market value in USD terms (in contrast to the flat or slightly negative growth rate in diagnosed lung cancer cases), we also expect the segment addressing LCC management to experience growth in USD value.

Factors contributing to our LCC market growth assumption include advancements in treatment options, increased awareness and diagnosis rates and a **growing emphasis on improving the quality of life for patients**. Whilst verifiable figures for the LCC management segment are notable by their absence, drawing inference from the broader lung cancer market's USD value CAGR of 8.3%, we anticipate a significant increase in market value for LCC over the next decade. In turn this could lead to a significant expansion of the total US lung cancer therapeutic market value (by adding a better defined new segment).

New market, new growth.

Our key inference is that the US lung cancer cough market represents a meaningful USD value component of the overall lung cancer therapeutics landscape. **We infer that there exists a substantial opportunity for investment and development in effective LCC management** (therapy/palliative) solutions for enhanced patient outcomes and meaningfully improved quality of life.

Exhibit 7: **US Lung Cancer Cough Market [ACF Est.] $14.5-16bn 2034E**



Differences in forecast starting values are based on different price assumptions for treatment. In our low case assumption the price assumption is USD 4,000 per patient per month. In our high case scenario we take the midpoint value of USD 6,000 per patient per month from the market range of therapies between USD 3,000 and USD 9,000 per patient per month.

Our low case scenario assumes a CAGR of 7.99% and therapeutic value generation, more or less in line with the expected growth rate over the period for the overall lung cancer market. Our high case scenario assumes the main driver in value is inflation (no additional value generation achieved) and our assumptions equate to a CAGR of 4.64%.

Sources: ACF Estimates, ACF Graphics,.

LCC Addressable Market Comparisons

Typical Addressable Market Proportions - For targeted therapies: 10–25% of total lung cancer cases. For immunotherapies: 40–60% of advanced NSCLC cases. In contrast for supportive therapies (e.g., lung cancer cough management): 57%–80% of patients, given nonspecific eligibility.

Epidermal growth factor receptor (EGFR) inhibitors are medications targeting the EGFR, a cell surface protein associated with cell growth and division. EGFR inhibitors best known use is in lung cancer treatment, where there are elevated levels of EGFR, e.g., in NSCLC, and also in pancreatic cancer, breast cancer, and colorectal cancer. There are two types of EGFR inhibitors – Tyrosine Kinase Inhibitors (TKIs) and Monoclonal Antibodies (mAbs) – they have different modes of action and both can be very effective in cancers with specific EGFR mutations.

Anaplastic lymphoma kinase (ALK) inhibitors target the ALK protein, blocking its activity and preventing cancer cell growth and spread, where there are mutations in the ALK gene e.g., in NSCLC. ALK inhibitors are a late stage NSCLC therapy and can deliver significant tumour shrinkage and survival improvements. ALK inhibitors have been subject to resistance. Lorlatnib (Lorbrena) can be prescribed to overcome resistance to earlier generation ALK inhibitors.

PD-1 inhibitors are cancer immune checkpoint inhibitors that target the programmed cell death protein 1 (PD-1), a checkpoint protein on immune system T-cells. PD-1 acts as an "off switch" to help prevent the immune system from attacking the body. Some cancer cells exploit this mechanism to avoid being attacked by the immune system. Therapies such as pembrolizumab (Keytruda) and nivolumab (Opdivo), block the interaction between PD-1 on T cells and its ligand PD-L1 on cancer cells. This prevents the "off" signal from being sent, allowing T cells to recognize and attack cancer cells. By blocking PD-1, these inhibitors enhance the body's own immune response against cancer cells.

Addressable Market for LCC -The addressable portion of the lung cancer market for a given therapy typically depends on several factors, including the therapy's mechanism of action, target population, approval status, and market dynamics. Historically, the following trends have been observed:

1. Segmentation by Lung Cancer Type - Lung cancer is divided into two main types: Non-Small Cell Lung Cancer (NSCLC) (~85% of cases) and Small Cell Lung Cancer (SCLC) (~15% of cases). *Similarly, LCC therapies may theoretically be applicable to 57% to 80% of patients depending on disease progression.*

Lung cancer therapies are often developed specifically for one subtype, which can limit the addressable population. For example, targeted therapies such as EGFR inhibitors or ALK inhibitors may only apply to 10-15% of NSCLC patients. *In contrast LCC therapies may theoretically be applicable to 57% to 80% of patients depending on disease progression.*

Immunotherapies, such as PD-1/PD-L1 inhibitors, have broader applicability but are still dependent on biomarker testing. Immunotherapies (e.g., pembrolizumab) and biomarkers, such as PD-L1 expression, determine eligibility and typically suggest 50–70% of advanced NSCLC cases can be addressed. **In contrast the application of LCC therapies appears not to be constricted by cancer type.** LCC is evenly distributed across patients irrespective of lung cancer type. *Similarly, LCC therapies may theoretically be applicable to 57% to 80% of patients depending on disease progression.*

2. Biomarker-Based Approvals - The rise of precision medicine points to therapies that are increasingly tailored to patients with specific biomarkers (e.g., EGFR mutations, ALK rearrangements). As a result, targeted therapies may have the potential to address 20–30% of the total NSCLC market. *LCC therapies may theoretically be applicable to 57% to 80% of patients.*

3. Treatment Stage - **Early-Stage Lung Cancer**: Less addressable for most therapies due to surgical or radiation-first approaches. **Advanced/Metastatic Lung Cancer**: Constitutes a larger portion of the market, as systemic therapies (targeted therapies, chemotherapy, immunotherapy) dominate treatment. *LCC therapies are in higher theoretical demand with a higher addressable market, the more advanced a patient's lung cancer becomes.*

4. Economic and Regulatory Factors - Insurance coverage and reimbursement policies affect access to therapies including supportive care for LCC, which can reduce the practical addressable market even for approved therapies. Therapies approved under restricted or accelerated pathways may initially address a small portion of the lung cancer market until expanded indications are achieved. These restrictions could be considered supportive for any biotech or pharmaceutical company explicitly targeting LCC, essentially creating an opportunity or possibility for leapfrogging competitors that consider LCC a secondary indication for a primary lung cancer therapy designation.

LCC Addressable Market – Other Factors

Factors Affecting the Addressable LCC Market

1. Prevalence of LCC Among Lung Cancer Patients - **Overall prevalence**: Studies show that 57–65% of lung cancer patients experience LCC as a symptom.
Stages of the disease: LCC is more common in advanced or metastatic stages due to tumour growth and its effect on airways. **Early-stage lung cancer**: LCC prevalence is lower but still clinically significant. **Advanced-stage lung cancer**: Prevalence can reach 75%-80% in symptomatic patients.

2. Demographic and Clinical Factors - The likelihood of a patient experiencing and seeking treatment for lung cancer cough are governed by Demographics and Treatment-seeking behaviour. **Demographics** - LCC prevalence, as we have observed in this thematic, shows no significant difference by sex or age but is often more severe in smokers and patients with coexisting respiratory conditions. **Treatment-seeking behaviour** - Patients in palliative care or symptomatic management (a majority of advanced cases) are more likely to seek LCC relief.

3. Therapeutic Modalities – **Pharmacological therapies** for lung cancer cough include pharmacological therapies, antitussive agents (opioid and non-opioid), corticosteroids, and inhaled therapies. **Non-pharmacological interventions** include radiation therapy or endobronchial interventions targeting tumours causing LCC. **Complementary therapies** include palliative and supportive care for symptom management.

Theoretical Addressable Market by Modality - Pharmacological therapies target 50–70% of symptomatic LCC patients. Non-pharmacological interventions address (20–30%) due to the invasive nature or cost. Complementary therapies are widely applicable and can address potentially 80%+ of advanced LCC cases, at lower cost.

4. Economic and Access Considerations - **Reimbursement and coverage** - Symptom-relief therapies often fall under broader palliative care coverage, meaning fewer reimbursement and coverage restrictions and so an inferred larger addressable population. **Patient prioritization** - Because LCC directly impacts quality of life, patients and caregivers are more likely to prioritize its management.

5. Practical Addressable Market – The total LCC population i.e. symptomatic with cough is 57–65% of early diagnosis lung cancer patients, irrespective of type or sex. Of this LCC symptomatic population, currently 70–80% are candidates for pharmacological or non-invasive symptom-relief therapies, equating to 40–65% of the total lung cancer population. This percentage increases beyond 70% in late-stage progression, where LCC relief is critical for palliative care.

Comparison with Curative Therapies - Unlike curative therapies (of which there are currently zero definitive options), symptom-relief therapies typically address a larger percentage of a cancer population because their eligibility is not tied to biomarkers or specific tumour characteristics. Therefore, currently, the LCC market is focused on delivery of symptomatic management.

LCC New Therapy Market Share Scenarios

Transformative therapies: Capture 60–80% of the addressable market at peak share due to strong differentiation.

Marginal therapies: Stabilize at 20–30% of the addressable market, primarily influenced by pricing and niche applicability.

The market share development for a new therapy depends significantly on its clinical profile, competitive differentiation, pricing strategy, and adoption rate by healthcare providers and patients. Specifically for the lung cancer market:

Transformative Therapies - If a new therapy demonstrates substantial improvements over existing options (e.g., improved survival rates, reduced side effects, or is addressing previously unmet needs like effective LCC alleviation), its market share growth typically follows an accelerated trajectory as described below.

***Transformative Therapy* Year 1–2: Initial Adoption** - Rapid adoption in clinical practice if the therapy achieves breakthrough designation, FDA fast-track approval, or EMA conditional approval. Target market adoption focuses initially on patients with the most urgent needs, such as advanced-stage lung cancer patients or those for which current treatments are ineffective. Market Share: Such therapies typically capture 10–25% of the addressable market as providers and patients assess the real-world effectiveness and safety of the new therapy.

***Transformative Therapy* Year 3–5: Rapid Growth** - Clinical Guidelines – the therapy is included in treatment guidelines (e.g., NCCN, ASCO), which has a marked effect on driving adoption. Payer Reimbursement - Comprehensive insurance coverage and favourable health technology assessments accelerate uptake. Market Share: Can reach 40–60% of the addressable market within 5 years if the therapy proves to be a clear clinical breakthrough.

***Transformative Therapy* Year 6–10: Market Penetration Stabilizes** – Competition - New competitors may enter the market, slightly eroding the initial or first mover advantage. Real-World Evidence - Continued post-marketing studies reinforce long-term safety and efficacy trends, solidifying the new therapy's position. Peak Share: Therapy reaches 60–80% of the addressable market for that indication, depending on its ability to maintain differentiation.

Marginally Beneficial Alternative Therapies - For a therapy offering incremental benefits over current options, market penetration is typically slower and more limited, as payers and providers prioritize cost-effectiveness and added clinical value.

***Marginal Therapy* Year 1–2: Slow Adoption** - Regulatory Barriers: Without compelling efficacy or quality-of-life benefits, reimbursement decisions may be delayed or contingent on price negotiations. Early Adoption – A therapy is used primarily in niche populations, such as patients that are intolerant to existing therapies or those seeking marginal symptom relief. Market Share: The marginally beneficial therapy typically captures 5–10% of the addressable market as initial adoption is cautious.

Transformative therapies: Capture 60–80% of the addressable market at peak share due to strong differentiation.

Marginal therapies: Stabilize at 20–30% of the addressable market, primarily influenced by pricing and niche applicability.

Examples of LC therapies without known or recognized LCC indications with estimated monthly cost in USD pppm:

Tagrisso (Osimertinib), Astra, USD 16,500; Imdeltra (Tarlatamab) Amgen, USD 3,000; Lumakras (Taxotere), Sanofi, USD 2,600; Hycamtin (Topotecan), Glaxo, USD 5,078.

***Marginal Therapy* Year 3–5: Moderate Growth -** Differentiation: Growth depends on factors like better tolerability, fewer side effects, or convenience (e.g., oral administration over infusion). Market Access: Broader adoption if cost-effectiveness data shows greater value in comparison to existing therapies, or pricing competes effectively with generics and biosimilars. Market Share: Marginal therapy grows to 15–25% of the addressable market if the associated benefits of the marginal therapy are sufficient to justify switching or expanding usage.

***Marginal Therapy* Year 6–10: Limited Peak Penetration -** Competitive Pressure: Entry of other marginal therapies limits market growth potential by creating buyer confusion or choice. Price Erosion: Generic or biosimilar versions may enter, reducing the branded marginal therapy's market share. Peak Share: Stabilizes at 20–30% of the addressable market unless significant additional benefits emerge from post-marketing studies.

Factors Influencing both Transformative and Marginal Therapy Market Scenarios:

1. Market Education - Significant improvement therapies see faster adoption if paired with robust physician education and marketing. Marginal therapies depend more on payer-driven decisions and price competitiveness.

2. Pricing Strategy - Premium pricing for transformative therapies often requires significant payer negotiations but can command high shares if the value can be convincingly demonstrated. Marginal therapies need competitive pricing to incentivize adoption.

3. Real-World Data - Positive real-world evidence accelerates growth for significant therapies and helps justify continued use of marginal therapies.

4. Patient Advocacy - For therapies targeting symptom relief (e.g., LCC), patient advocacy groups can help expand awareness and adoption for both transformative and marginal options.

Competitive Landscape

Exhibit 8: **Market character - key players and a clear unmet need**

Company Name	Tkr	EV USD (bn)	EV/ EBITDA	Compound Name	Therapy or Palliative	Summary description for Lung Cancer Cough (LCC)
Eli Lilly	LLY	815.01	47.5x	Various (e.g., Olumiant)	**Palliative**	Therapies used off-label to manage lung cancer cough symptoms in cancer patients.
Merck & Co.	MRK	200.91	10.3x	Keytruda (pembrolizumab)	**Therapy**	Keytruda - an immunotherapy for cancers including NSCLC. Effective treatment may lead to LCC amelioration.
AstraZeneca	AZN	431.26	13.3x	Tagrisso (osimertinib)	**Therapy**	Tagrisso is a targeted therapy for NSCLC with EGFR mutations. Effective cancer treatment can alleviate LCC.
Novartis	NVS	219.57	10.4x	Various (e.g., Promacta)	**Palliative**	Drugs offered to manage symptoms in cancer patients, including LCC.
Pfizer	PFE	129.20	11.7x	Various (e.g., Toviaz)	**Palliative**	Therapies used off-label to manage cough symptoms in cancer patients.
Boehringer Ingelheim	Private	130[E]	NA	Gilotrif (afatinib)	**Therapy**	Gilotrif is a therapy for NSCLC with specific EGFR mutations. By targeting the cancer, it may help reduce cough.
GlaxoSmithKline	GSK	75.97	10.2x	Various (e.g., Nucala)	**Palliative**	Provides therapies that may help manage respiratory symptoms, including LCC, in cancer patients.
Teva Pharma	TEVA	16.87	51.6x	Various (e.g., Codeine)	**Palliative**	Generics such as codeine, prescribed to manage LCC in patients.
Summit Therapeutics	SMMT	27.07	NM	Ivonescimab	**Therapy**	Ivonescimab is an experimental therapy for NSCLC, may also alleviate LCC.
Merus N.V.	MRUS	3.06	NM	Bizengri	**Therapy**	Targets NRG1 gene fusions in cancers, including NSCLC. May (potentially) result in reduced LCC.

[E] = Estimated

Sources: ACF Equity Research; ACF Lung Cancer Cough Therapies and Palliatives Competitive Landscape 20032025; Company reports.

Potential Molecular Antagonist Targets – under investigation include: **P2X3 Receptor Antagonists**, which inhibit purinergic receptors involved in LCC reflex sensitization; **Neurokinin-1 Receptor (NK1R) Antagonists**, which block substance P pathways; **TRPV1 Antagonists**, which are involved in capsaicin-sensitive C-fibre activation.

Biovara Specific LCC Investment Case

In order to illuminate the investment case for the LCC market we have taken private healthcare/biotech aprepitant reformulator Biovara Limited to establish an indicative or potential NPV contribution of an indication for lung cancer cough. Our low value potential NPV contribution to Biovara is the based upon a lowest rational value, which assumes a going concern scenario. Similarly, our approach means that our high value NPV constitutes the lowest reasonable or rational high value. All financial values are in USD, and we focus only on the potential of the US opportunity. Specific publicly available data for the market value for LCC treatments is limited. We used a series of statistical and analytical techniques and read-through approaches to establish our axioms and valuation assumptions.

General Axioms [7]

For our NPV low and high scenarios for Biovara's possible LCC therapy we have 7 general axioms we have applied to both our specific NPV scenarios:

1.We have assumed a competitive market. Whilst we infer that Biovara may be able to deliver a transformative LCC therapy, we have assumed that because lung cancer cough biochemistry is relatively poorly understood and there are a range of therapies in the market that are used to address LCC as a secondary indication, it could initially be difficult to demonstrate transformative efficacy through peer reviewed academic papers and this may slow initial market uptake.

Note that whilst consensus forecasts are projecting a very modest decline in lung cancer (LC) cases, the Lung Cancer Cough (LCC) market remains a clear unmet need and would be a growth market within LC.

2.The US lung cancer cough market represents a vital component of the overall lung cancer therapeutics landscape. With an increasing focus on quality of life from regulators, we assess the LCC market has a higher probability of becoming more valuable rather than less valuable as a constituent of the total lung cancer therapy market.

3.We have assumed that prescription medications for suppressing LCC can cost over USD 4,000 pcm - Therapies already marketed that can also alleviate LCC can cost in excess of USD 9,000 pcm. Low intensity palliative care averages around USD 3,000 pcm.

4.We have assumed Biovara's therapy sells at $4,000 pcm, the lower end of the $3,000 pcm to USD 9,000 pcm range, it could clearly be a lot higher if the therapy is a 'knockout' or transformative improvement on what is currently available.

5.We have assumed that the incidence of lung cancer in the US neither increases nor declines over our 10-year projection i.e., ~116k men and 118k women per annum. Furthermore, we have assumed that the type of lung cancer (NSCLC, 85% of cases and SCLC, 15% of cases), and that age and sex bare little relevance to the probability of lung cancer cough.

6.We have assumed that 60% of lung cancer patients suffer from lung cancer cough (LCC) - this is around the mid-range of recent market studies.

7.We have assumed that the majority of patients are 65 or older suggesting that they will still have medical insurance or will be in a position to be self-funded and have or retain agency to make buying decisions in respect of therapies.

Exhibit 9: **Biovara NPV High Low LCC Therapy Potential**

Key Specific Assumptions US LCC Market	Scenario NPV Low - Marginal Therapy	Scenario NPV High - Transformative Therapy
Lung Cancer Incidences p.a.	234,580	234,580
Current Est. Monthly treatment cost per patient US$(	4.000	4.000
Year 10 Monthly treatment cost per patient US$(k)	5.120	5.120
CAGR annual (for cost per patient per month)	2.5%	2.5%
LLC Suffers as % of LC	60%	60%
Implied # US LCC Sufferers p.a.	140,748	140,748
Current Est. Market Value Monthly (Year 1) US$(m)	563	563
Forecast Market Value Monthly (Year 10) US$(m)	721	721
Addressable LCC sufferers %	70%	70%
Addressable LCC Sufferers p.a.	98,524	98,524
Current Est. Market Value Monthly (Year 1) US$(m)	394	394
Forecast Market Value Monthly (Year 10) US$(m)	504	504
Year 1 Market Penetration %	5%	8%
Year 10 Peak Market Penetration %	20%	70%
Remaining R&D Capex US$(m)	10	20
FCF Margin %	20%	20%
WACC %	20%	20%
NPV US$ (m)	377.92	937.90
Phase Stage Assumption	2	2
Risk Adjustment based on Phase Stage Median Value	50%	50%
Potential NPV Contribution to Biovara US$(m)	**189**	**469**

Sources: ACF Equity Research; ACF Lung Cancer Market Model 25032025; ACF Oxilio research; Oxilio company reports;

Biovara is addressing an unmet medical need suffered by circa 80% of late stage lung cancer patients and 57-65% of early stage lung cancer patients.

As per our competitive landscape exhibit, most therapies appear to be primarily indicated for LC, but are also prescribed for LCC without any definitive efficacy data. This means that, in effect, there are no effective or specific therapies for LCC.

Biovara points out that most or all of the therapies applied to LCC currently come with significant adverse effects.

Biovara's confirmatory clinical trial will be informed and advised by those physicians who ran the earlier 'physician-led' studies which demonstrated the efficacy of aprepitant for treating LCC.

Whilst Biovara Limited (Biovara) is 100% owned by Oxilio Limited (Oxilio) it is separately managed and all Biovara's relevant IP is wholly owned by Biovara with a 20+ year life span. The implication is significant and early investor returns are available.

Biovara likely exits are licensing or sale of Biovara's LCC aprepitant based reformulation therapy within 24 months of successful funding.

Note that there is in practice little if any correlation between efficacity/novelty and therapy pricing, suggesting that Biovara's LCC therapy would likely tend towards our higher NPV rather than our lower value. (Cancer Drug Price and Novelty in Mechanism of Action - Miloš D. Miljković, MD1; Jordan Tuia, BA2; Timothée Olivier, MD3; et al; publication Pharmacy and Clinical Pharmacology; JAMA Netw Open. 2023;6(12):e2347006. doi:10.1001/jamanetworkopen.2023.47006

Biovara Limited (Biovara) is 100% owned by Oxilio Limited (Oxilio). Biovara holds its own Intellectual property and is separately managed from Oxilio.

Whilst we have made a series of very conservative baseline assumptions for both first pass NPV scenarios for value that might accrue to Biovara on successful licensing and some of these assumptions, such as therapy price, could be viewed differently, we have some cause to infer that following a full company analysis process, we could reach significantly higher NPVs for both low and high scenarios. However, it should also be highlighted to investors that there is potential that these NPV scenarios could be lower after a full analysis than our current analysis suggests. Clearly if no license is obtained then a negative NPV is likely to accrue to Biovara for the LCC R&D investment.

The global lung cancer (LC) therapeutics market consensus value was approximately USD ~30bn in 2023. Market consensus projections suggest the value may reach USD >71bn by 2034, a compound annual growth rate (CAGR) of 8.2% over the 10 year forecast period, whilst we have used an effective CAGR of 2.5% in the USD value for LCC over the same forecast period, when calculating Biovara's potential NPV accretion.

Micro/Small Cap Investment Risks and Mitigation

Risks:

Clinical Trial Failures - Early-stage companies face significant risks in clinical trials, where a single failure can undermine valuations in a 0:1 sum game investment scenario.

Regulatory Uncertainty - FDA and EMA approvals are stringent, and without fast track approval, delays or rejections can limit commercialisation opportunities.

Funding Challenges - Nano, micros and small-cap firms often rely on equity raises, diluting shareholder value during early-stage development. These *dilution events* often feel very painful to retail investors on whom nano, micro and small caps often depend. In turn these dilution events can create a crisis situation that may progress to the courts leading to irretrievably damaged management credibility. Nano, micro and small caps are disproportionately reliant on their *executive management* teams compared to mid, large and mega caps.

Mitigation Strategies:

Diversification - Invest in a basket of nano, micro and small-cap biotech firms to spread risk across multiple candidates and technologies.

Research coverage - Avoid companies with nil research coverage: Whilst investment research coverage does not guarantee outperformance, a lack of research coverage guarantees underperformance and undervaluation and often failure in the longer term.

Focus on Catalysts - Identify companies with upcoming regulatory milestones or clinical trial readouts to align investments with near-term value drivers.

Monitor Partnerships - Look for firms with strong collaborations with larger biotech or pharmaceutical companies, as these partnerships reduce development and distribution risk and provide a natural exit strategy from PII trials results onwards.

Investment Conclusions:

Transformative Potential in a High-Growth Sector - The nano, micro and small-cap biotech space offers significant opportunities for investors to engage in a sub-segment undergoing technological innovation with high take out premiums. Whilst risk is inherently higher in nano to small cap biotech when compared to mid, large and mega cap players, the crystallised valuation effect of breakthrough therapies that secure FDA or EMA approval and disrupt traditional treatment paradigms can provide super-normal returns.

By strategically investing in the healthcare/biotech cancer sector, investors can position themselves to capitalize on a new and so growth healthcare sub-sector.

Peer Groups

Exhibit 10: Peer group metrics mega cap LCC therapies

TTM Metrics / Company Name	Market	Tkr	MCAP US$(m)	Rev / Per Head	FCF / Per Head	RoA	RoE	RoIC	β 5yr	EV / FCF	P/ book
Eli Lilly	**XNYS**	**LLY**	**815,015**	**958,355**	**26,328**	**15.86%**	**77.11%**	**52.92%**	**0.01**	**683.2x**	**52.5x**
AstraZeneca	XLON	AZN	575,344	573,415	77,147	15.35%	17.76%	10.30%	0.25	82.5x	785.9x
Novartis	XNYS	NVS	219,571	681,602	181,925	23.61%	28.30%	15.73%	0.55	17.3x	5.0x
Merck	XNYS	MRK	200,909	855,573	241,280	21.65%	39.18%	21.35%	0.42	12.4x	4.3x
Pfizer	XNYS	PFE	129,196	785,519	121,420	8.96%	8.89%	8.44%	0.60	19.5x	1.4x
Average				724,027	155,443	17.39%	23.53%	13.96%	0.45	32.9x	199.2x
Median				733,560	151,672	18.50%	23.03%	13.02%	0.48	18.4x	4.6x

Sources: ACF Equity Research; Refinitiv.

Exhibit 11: Peer group metrics large/mid cap LCC therapies

TTM Metrics / Company Name	Market	Tkr	MCAP US$(m)	Rev / Per Head	FCF / Per Head	RoA	RoE	RoIC	β 5yr	EV / FCF	P/ book
GSK	**XLON**	**GSK**	**101,357**	**457,183**	**48,405**	**6.97%**	**18.43%**	**10.27%**	**0.01**	**34.5x**	**429.9x**
Teva	XNYS	TEVA	16,867	488,109	22,100	-8.29%	-26.12%	7.27%	0.72	42.3x	2.8x
Summit Therapeutics	XNAS	SMMT	27,071	0	-893,665	-51.03%	-83.05%	-53.75%	-0.46	N/M	61.8x
Merus	XNAS	MRUS	3,065	138,973	-721,169	-27.57%	-35.19%	-40.55%	1.03	N/M	4.1x
Average				209,027	N/M	N/M	N/M	N/M	0.43	42.3x	22.9x
Median				138,973	N/M	N/M	N/M	N/M	0.72	42.3x	4.1x

Sources: ACF Equity Research; Refinitiv.

Companies Referenced In Report

Exhibit 12: Companies mentioned in report

Companies Mentioned in this report	Tkr	Exchange	EV ($bn)	Reporting Currency	52 wk hi	52 wk lo	Previous Close	% from 52 wk High
Eli Lilly	LLY	NYSE	845.4	USD	972.5	677.1	829.4	14.7%
AstraZeneca	AZN	NASDAQ	455.9	USD	87.7	61.2	68.5	21.9%
Novartis	NVS	NYSE	239.4	USD	120.9	96.1	110.1	8.9%
Merck	MRK	NYSE	224.8	USD	134.6	75.9	78.7	41.5%
Amgen	AMGN	NASDAQ	198.5	USD	346.9	253.3	277.9	19.9%
Pfizer	PFE	NYSE	191.8	USD	31.5	20.9	22.4	29.0%
Sanofi	SAN	NYSE	115.5	EUR	7.2	4.3	7.1	0.8%
GlaxoSmithKline	GSK	NYSE	70.5	GBP	45.9	31.7	37.0	19.4%
Teva Pharmaceuticals	TEVA	NYSE	31.6	USD	22.8	12.5	14.3	37.3%
Summit Therapeutics	SMMT	NASDAQ	27.0	USD	36.9	2.1	33.2	10.0%
Merus N.V.	MRUS	NASDAQ	2.8	USD	61.6	33.2	41.8	32.1%
Oxilio	Private	Private	0.35	Private	Private	Private	Private	Private
Biovara	Private	Private	Private	Private	Private	Private	Private	Private
Boehringer Ingelheim	Private	Private	130[E]	Private	Private	Private	Private	Private

[E] = Estimated

Sources: ACF Equity Research

Notes [Intentionally Blank]

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ACF Equity Research Limited, 125 Old Broad Street, London, EC2N 1AR, U.K.
Tel: +44 (020) 7558 8974
Website: www.acfequityresearch.com