

The background of the cover features a medical theme. On the left, several white and grey capsules are scattered over a grid pattern. To the right, a portion of an ECG (heart rate) monitor is visible, showing a blue line graph with peaks and troughs. The labels 'V2' and 'V3' are printed on the grid. A large, diagonal, semi-transparent watermark with the word 'SAMPLE' in a bold, sans-serif font runs across the center of the image from the bottom-left towards the top-right.

GlobalData» OpportunityAnalyzer

**AMYOTROPHIC LATERAL SCLEROSIS (ALS) –
OPPORTUNITY ANALYSIS AND FORECASTS TO 2018**

Executive Summary

A Steady Decline is Expected for the ALS Market from 2013 to 2018

The table below presents the key metrics for amyotrophic lateral sclerosis (ALS) in the seven major pharmaceutical markets (7MM) (US, France, Germany, Italy, Spain, UK, and Japan) covered in this report during the forecast period from 2013 to 2018.

GlobalData estimates that the ALS market across the 7MM was worth \$64m in 2013, and will fall to \$38m by 2018, at a negative Compound Annual Growth Rate (CAGR) of 10.05%. The US market will continue to generate the highest yearly sales throughout the 2013–2018 forecast period, but sales growth will decline at a negative CAGR of 16.10% due to the patent expiration of its only ALS-approved therapy, Rilutek (riluzole). In the 5EU and Japan, the ALS drug market will reflect negative CAGRs of 3.85% and 3.08%, respectively.

| ALS: Key Metrics in the 7MM, 2013–2018 | |
|---|--------------|
| 2013 Epidemiology | |
| Diagnosed prevalent population (≥40 years) | 23,671 |
| 2013 Market Sales | |
| US | \$38m |
| 5EU | \$10m |
| Japan | \$16m |
| Total | \$64m |
| Pipeline Assessment | |
| Number of drugs in Phase III | 5 |
| Key Events (2013–2018) | |
| 2013: Rilutek (riluzole) patent expires (US, Japan) | ↓↓↓ |
| 2015: Launch of Methycobal (mecobalamin) (Japan) | ↑ |
| 2016: Launch of AB-1010 (masitinib) (US, 5EU) | ↑ |
| 2016: Launch of tirasemtiv (US, 5EU) | ↑ |
| 2016: Launch of Radicut (edaravone) (Japan) | ↑ |
| 2018 Market Sales | |
| US | \$16m |
| 5EU | \$9m |
| Japan | \$13m |
| Total | \$38m |
| Source: GlobalData | |
| 7MM = US, France, Germany, Italy, Spain, UK, and Japan; 5EU = France, Germany, Italy, Spain, and UK | |

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The major barriers for the ALS market over the forecast period are as follows:

- The patent expiration of Rilutek in the US in 2013: As the only approved therapy in the US, the reduction in the market size over the forecast period is largely representative of the decline in Rilutek sales due to generic erosion. Further market losses resulting from the patent expiration of Rilutek in the EU in 2012, and in Japan in 2013, will cause the ALS market to shrink across the 7MM. The generic availability of Rilutek, which is the current standard of care, will entirely reshape the ALS market landscape.
- Poor transferability of results between animal studies and human trials: while SOD1 mouse models have been instrumental in the understanding of ALS and the development of Rilutek, the positive results observed in animal studies have largely failed to carry over in human trials.
- A lack of biomarkers to diagnose and stage patients: Long delays between the onset of symptoms and establishing a formal diagnosis are common in ALS, which, in the early stages may be difficult to discern from other motor neuron diseases (MNDs).
- Inconsistent policies regarding early access to orphan drugs in the 5EU limit the availability of these drugs: Germany allows for easy access to approved orphan drugs, but does not allow early access to these medications for patients with rare diseases, such as ALS. In the UK, patients are allowed early access to orphan drugs prior to approval, but the process is considered slow and expensive.
- Poor understanding of the biology of ALS: Several drugs have advanced to late-stage clinical trials; however, only one medication has received approval by the Food and Drug Administration (FDA), Rilutek, indicating the inability to identify only the targets that will elicit therapeutic effects.

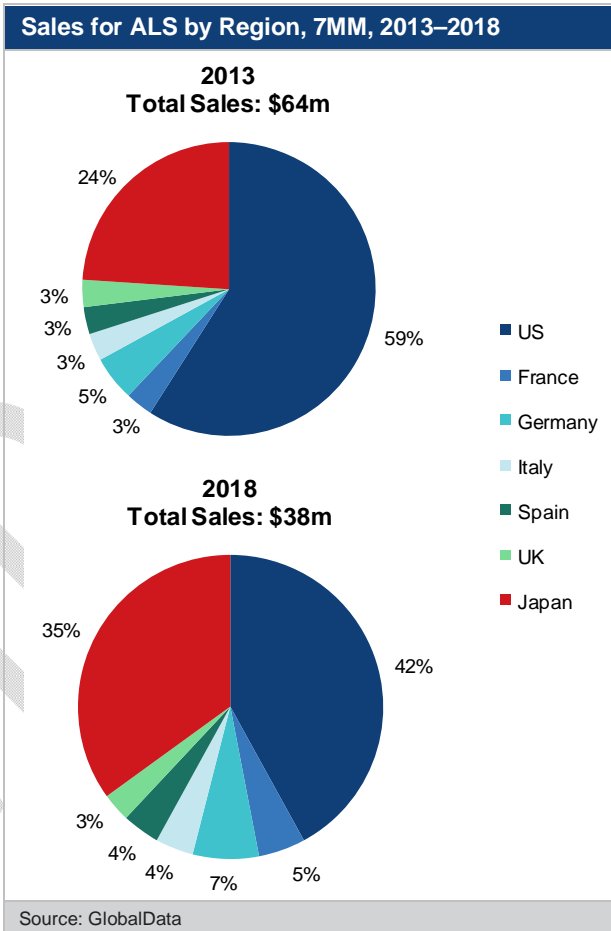
The major drivers of the growth of the ALS market over the forecast period are as follows:

- Promotion of drug development in orphan diseases: Through efforts such as tax credits, research grants, accelerated marketing approval pathways, and early access by governments in the US, 5EU, and Japan.
- Advances in disease modelling: With special attention to TDP-43 and C9orf72, new ALS animal models will identify new therapeutic targets, and will renew interest in ALS by the pharmaceutical industry.

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- Nearly all ALS patients are offered Rilutek, a glutamate-based treatment that can extend survival by three months. Most patients will also receive off-label medications to treat symptoms such as excessive saliva, constipation, muscle cramps, insomnia and daytime fatigue, and emotional lability. Psychosocial care, nutrition support, speech therapy, and other interventions are recommended to help support patients as they approach the end of their life. With a shortage of treatment options and increasing standards for quality of life (QOL) for patients with terminal diseases, government regulators in the 7MM are shifting their policies to promote drug development for rare diseases like ALS.
- The recent failures of the previously promising Phase III pipeline compounds dexpramipexole, olesoxime, ceftriaxone, and talampanel has restricted the growth of and interest in the ALS market. Talampanel, which was under development for the treatment of ALS, glioblastoma multiforme, recurrent malignant glioma, Parkinson's disease, and partial seizure disorders, received an orphan drug designation in the US and 5EU in 2008 and 2009, respectively. In May 2010, Teva, the developer of talampanel, announced that the drug had failed to meet its efficacy endpoints, and that the development of the product in ALS had been discontinued.

The figure below illustrates the sales for ALS by region in the 7MM during the forecast period.



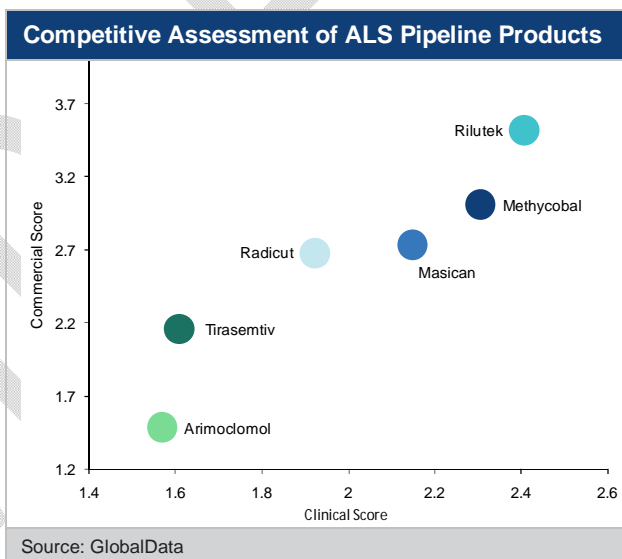
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Drugs with Unproven Mechanisms of Action are Poised to Enter the ALS Market

Due to the diversity of ALS etiologies and patients' unmet needs, there is a drastic need for new therapies that can alleviate the symptoms of the disease and stop or reverse its pathology. The unmet needs in ALS are reflected in the limited diversity of the current pipeline. A varied set of mechanisms of action is being explored, but no dominant theories have emerged to help guide drug development. AB Science's AB-1010 (masitinib), an oral tyrosine kinase inhibitor (TKI), targets the inflammatory processes that are believed to contribute to the pathogenesis of ALS, while Cytokinetics' tirasemtiv aims to improve muscle strength through fast-muscle troponin activation. Once marketed, these medications will continue to supplement the anticholinergic therapy, Rilutek, and off-label therapies, which will provide greater relief of symptoms, but will fail to reverse the course of the disease. The diversity of patients with ALS, as well as the drug currently used in its treatment, makes it challenging to compare these drugs with one another in terms of their clinical and commercial potential. For this reason, GlobalData compared the pipeline products against Rilutek, the only drug currently available for specifically for ALS across the 7MM, which requires twice-daily oral administration.

With few marketed options available, any new treatment for ALS will become central to the management of the disease, and will have fewer concerns with regard to tolerability and reimbursement if it can show that it is remarkably effective.

The figure below provides a competitive assessment of the ALS pipeline products.



A Disease-Modifying ALS Treatment that Prevents the Disease from Worsening Remains Elusive

At the heart of the unmet needs in the ALS market is the development of a cure and/or treatment options that are permanently able to prevent motor neuron damage. The efficacy of Rilutek can be limited by its side effects and interference from symptoms in the advanced stages of the disease, which, over time, can lead to poor patient

Executive Summary

compliance, as well as greater challenges in obtaining access to care.

Therefore, a therapy that has both a satisfactory short- and long-term safety profile and is disease-modifying is still needed. The route of administration, according to key opinion leaders (KOLs) interviewed by GlobalData, is not a primary concern facing the development of new ALS medications. Therefore, the pharmaceutical industry should continue to explore the development of drugs with diverse mechanisms of action and routes of administration, as any new addition to the market will be vital for the treatment of ALS patients.

What Do Physicians Think?

The KOLs interviewed by GlobalData had mixed opinions about the current ALS pipeline, as these drugs have failed to demonstrate their value as new options for the treatment of ALS patients in clinical trials.

“There are lot of treatments in trials right now for ALS, as both disease-modifying therapies and also as symptomatic treatments...there is also genetic treatments, as well, on the way, so I believe that, yes, we will have a different treatment in the next five years.”

US KOL February 2014

The KOLs acknowledged that a poor understanding of the disease and the lack of biomarkers has complicated diagnosis and disease-staging, and will need to be developed in order to increase the treatment armamentarium for ALS patients.

“The lack of knowledge of the underlying disease mechanisms is the biggest challenge. Related to that, we don’t have any markers that make it easy to study, to look at a drug activity. We need more specific pharmacodynamic markers of disease progression, better identification of targets for drugs, and ways of identifying whether the drug is engaged in the target.”

US KOL February 2014

“The diagnostic problem is a big one; it takes about one year for patients with ALS, from the time they develop the first symptom until they get the diagnosis, and they see an average of three different specialties on the way until they get the final diagnosis.”

US KOL February 2014

“Deciding [on] a staging system will make it easier for [conducting] clinical trials and to understand the disease”

EU KOL February 2014

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The KOLs identified issues about the reliance on SOD1 animal models of ALS, particularly the inability to replicate the benefits observed in animal studies in human trials.

“The animal model we have used is always the SOD1 mouse. We know that SOD only affects 3% of people with ALS, and 96% have TDP-43 ALS. So, I really wish to be treating TDP-43 nerves, or nerve that has TDP-43.”

UK KOL February 2014

“We learned a lot from [the] SOD1 mouse model; we learned [about] a lot of the mechanisms of [the] disease, and it’s still a valuable model to study mechanisms, but I don’t think we have seen any translation of success in the mouse model that actually can [be] translated into humans. There are a lot of medications that works [sic] on the mouse model, but never work on people, so that’s a huge limitation.”

US KOL February 2014

While disease-modifying therapies are ideal additions to the ALS drug market, the KOLs pointed out that medications that provide better symptomatic control will provide more comprehensive management of the disease and improve patient QOL.

“Altering [the] disease course is the holy grail, but there is a whole set of other potential treatments that could be very effective in changing function for the better.”

US KOL February 2014

“[The] major unmet needs that are not disease-modifying is [sic], (1) the treatment of muscle strength, (2) is the dry saliva in people with bulbar disorder, and (3) is [the] treatment of emotional lability.”

UK KOL February 2014

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Introduction

2 Introduction

2.1 Catalyst

The amyotrophic lateral sclerosis (ALS) treatment regimen is currently dominated by a single glutamate antagonist, Rilutek (riluzole). Over the last five to 10 years, the use of off-label medications has become routine in the treatment regimen for some patients for the alleviation of symptoms. However, since they are used off-label, reimbursement problems have meant that these treatment options have only been available to a small percentage of patients.

Currently, there are three novel drugs in Phase III clinical trials for the treatment of ALS in the US and 5EU: AB-1010 (masitinib), CK-2017357 (tirasemtiv), and arimoclomol (arimoclomol), and two in Japan: Radicut (edaravone) and Methycobal (mecobalamin). With unproven mechanisms of action in ALS, the introduction of these drugs into the treatment protocol will have a small immediate impact on the size of the ALS market during the forecast period, and will result in a shift towards the use of newly-available generic formulations of Rilutek. GlobalData anticipates that the market decline will continue beyond the forecast period, despite the launches of new products. Furthermore, the current Phase III pipeline products do not address the core unmet needs for ALS patients, such as salivary overproduction and muscle weakness. While these new products will significantly increase the treatment options for ALS patients, their impact on the level of care is indeterminate. After the forecast period, significant opportunities will still remain for products that are able to stop or reverse the root cause of the disease, improve symptoms, minimize invasive procedures, and prolong life. The most significant barrier to the growth of the ALS market will be a poor understanding of the complex biology of ALS, as well as the lack of biomarkers to aid in diagnosis and disease management. Furthermore, challenges to the reimbursement of new treatments will arise, especially in Europe, where cost-effectiveness is becoming an ever-increasing central issue in the drug approval process.

2.3 Upcoming Related Reports

- GlobalData (2014). Multiple Sclerosis. Global Drug Forecast and Market Analysis to 2023

Appendix

10.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports, and forecasts. Our analysis is supported by a 24/7 client support and analyst team. GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

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