About Datamonitor Healthcare
Bringing you a clearer, richer and more responsive view of the pharma & healthcare market.

Complete market coverage
Our independent research and analysis provides extensive coverage of major disease areas, companies and strategic issues, giving you the perspective to identify opportunities and threats arising from shifting market dynamics and the insights to respond with faster, more effective decision-making.

Unique expert capabilities
With teams located across developed and emerging pharma markets, we are uniquely placed to understand local healthcare trends and provide accurate and reliable recommendations. By working closely with our partners at MedTrack, Citeline, SCRIP Intelligence and Informa Healthcare, our experts are able to share data and resources to produce the most authoritative and robust market intelligence. With over 700 clients across the pharma and biotech industries, we are relied upon to provide strategic guidance, not only through published analysis, but also tailored support solutions.

Cutting-edge delivery
Available through single reports or via subscription to our state-of-the art online intelligence service that features intuitive design and interactive capabilities, our analysis offers the definitive platform to enhance your product management, market assessment and strategic planning.

Contact Us
For more information about our products or to arrange a demo of the our online service, please contact:
getcloser@datamonitorhealthcare.com

Disclaimer
All Rights Reserved.
No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publisher, Datamonitor Healthcare. The facts of this report are believed to be correct at the time of publication but cannot be guaranteed. Please note that the findings, conclusions and recommendations that Datamonitor Healthcare delivers will be based on information gathered in good faith from both primary and secondary sources, whose accuracy we are not always in a position to guarantee. As such, Datamonitor Healthcare can accept no liability whatsoever for actions taken based on any information that may subsequently prove to be incorrect.

For more information about our products or to arrange a demonstration of the our online service, please contact:
getcloser@datamonitorhealthcare.com
TABLE OF CONTENTS

4 PRODUCT PROFILES
4 ganaxolone: Epilepsy

LIST OF FIGURES

9 Figure 1: Ganaxolone for epilepsy – SWOT analysis
10 Figure 2: Datamonitor Healthcare’s drug assessment summary for ganaxolone in epilepsy
10 Figure 3: Datamonitor Healthcare’s drug assessment summary for ganaxolone in epilepsy

LIST OF TABLES

4 Table 1: Ganaxolone drug profile
7 Table 2: Ganaxolone Phase II/III data in epilepsy
PRODUCT PROFILES

ganaxolone: Epilepsy

PRODUCT PROFILE

Analyst Outlook

Marinus Pharmaceuticals intends to continue the clinical development of ganaxolone in status epilepticus and pediatric orphan indications, despite the failure of the Phase III trial evaluating the efficacy of the drug in patients with refractory partial-onset seizures. Pediatric orphan indications, including PCDH19 female epilepsy, represent high unmet needs given the limited therapies available. While ganaxolone’s weak efficacy profile is not encouraging for its other niche indications under investigation, Datamonitor Healthcare believes that Marinus Pharmaceuticals is betting on the scientific rationale supporting use in PCDH19 female epilepsy.

Drug Overview

Marinus Pharmaceuticals is developing ganaxolone, a first-in-class synthetic neurosteroid drug for the adjunctive treatment of status epilepticus and pediatric orphan indications. It is a structural analog of the endogenous steroid allopregnanolone, and as such, is a powerful positive allosteric modulator of the gamma-aminobutyric acid (GABA)-A receptor with comparable potency (Carter et al., 1997).

In June 2016, Marinus Pharmaceuticals announced its plans to discontinue the development of ganaxolone for adult partial-onset seizures following its failure to meet the primary endpoint in a Phase III study (ClinicalTrials.gov identifier: NCT01963208). Marinus Pharmaceuticals plans to focus its efforts on advancing ganaxolone in status epilepticus and other pediatric niche indications (Marinus Pharmaceuticals, 2016a).

Ganaxolone has orphan drug designation, both as an intravenous formulation for the treatment of status epilepticus and as a potential oral treatment for PCDH19 female epilepsy. Further clinical development in both of these indications is underway, in addition to a separate study in fragile X syndrome (Marinus Pharmaceuticals, 2015a; 2015b; 2016b).
DEVELOPMENT OVERVIEW

Ganaxolone’s weak efficacy in partial-onset seizures is further reiterated in a failed Phase III study

Marinus Pharmaceuticals has now completed two efficacy studies of ganaxolone as an adjunctive treatment for refractory partial-onset seizures in adults. Neither of these studies provided compelling evidence for the drug’s efficacy relative to other anti-epileptic drugs, resulting in Marinus’s decision to discontinue further development in this indication.

In June 2016, Marinus Pharmaceuticals announced topline results from a multinational Phase III study in adult partial-onset seizures, which randomized 179 patients to receive ganaxolone 1,800mg/day and 180 patients to receive placebo. The company reported that ganaxolone missed its primary endpoint of percent change in the 28-day seizure frequency from baseline, with a median percent reduction of partial-onset seizures of 21.28% in the ganaxolone arm compared to 10.25% with...
placebo (p=0.1537) during the titration and the 12-week treatment period (Marinus Pharmaceuticals, 2016a).

These results were somewhat consistent with the data from the placebo-controlled, randomized, Phase II clinical trial of adjunctive ganaxolone therapy for the treatment of refractory adult partial-onset seizures (Study 1042-0600; ClinicalTrials.gov identifier: NCT00465517). The study, which recruited 147 patients, reported that ganaxolone reduced weekly seizure frequency from baseline by 18% versus 2% for placebo over the 10-week treatment period (Biomedtracker, 2016; Bialer et al., 2013). While the study did meet its primary endpoint, ganaxolone's efficacy was modest in this study as well, and does not compare favorably with established comparator products (Bialer et al., 2013). Furthermore, the placebo response in Phase II was significantly lower than in the Phase III trial (2% versus 10%), and from previously conducted epilepsy studies, which could explain how ganaxolone achieved statistical significance to begin with. The consistent modest impact of ganaxolone in reducing refractory partial-onset seizures (18–21%) speaks to the weak clinical profile of the drug. In light of these findings, Marinus Pharmaceuticals decided to discontinue the development of ganaxolone in the treatment of refractory partial-onset seizures.

**Proof-of-concept Phase II study hints at efficacy in PCDH19 female pediatric epilepsy**

In October 2015, Marinus Pharmaceuticals announced topline results from its open-label Phase II proof-of-concept study evaluating ganaxolone as a treatment for PCDH19 female pediatric epilepsy patients. The primary endpoint was percentage change in seizure frequency per 28 days relative to baseline. Interim results indicated that five out of eight patients (63%) had a ≥50% improvement in monthly seizure reduction compared to baseline. In addition, improvements in behavior and cognitive skills in some patients have been reported. The full dataset is expected to be released during 2016 (Marinus Pharmaceuticals, 2015c; Biomedtracker, 2016). While these findings are encouraging, Datamonitor Healthcare believes that a larger double-blind study will need to be conducted before Marinus can fully establish the efficacy and safety of ganaxolone in the treatment of PCDH19 female pediatric epilepsy.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size</th>
<th>Target patients</th>
<th>Study design</th>
<th>Dosing tested and duration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01963208 (Phase III)</td>
<td></td>
<td>Adult patients with drug-resistant partial-onset seizures, on a stable regimen of one to three AEDs</td>
<td>Multicenter, double-blind, randomized, placebo-controlled trial followed by open-label treatment</td>
<td>Ganaxolone 1,800mg/day or placebo, twice daily; Duration: Eight-week baseline period; nine-week placebo-controlled treatment phase; 52-week open-label extension</td>
<td>Median percent reduction of partial onset seizures: Ganaxolone: 21.28% Placebo: 10.25% (P=0.1537)</td>
<td>Marinus Pharmaceuticals, 2016a</td>
</tr>
<tr>
<td>1042-0600 (NCT00465517) (Phase II)</td>
<td>147</td>
<td>Patients aged 18–69 years, diagnosed with uncontrolled partial-onset seizures with or without secondary generalized seizures</td>
<td>Double-blind, randomized, placebo-controlled, safety/efficacy</td>
<td>Ganaxolone 200–500mg three times daily or placebo, for an eight-week baseline period, two-week titration, and eight-week maintenance period</td>
<td>Reduction in weekly seizure frequency: Ganaxolone: 18% Placebo: 2% (p=0.014)</td>
<td>ClinicalTrials.gov; Bialer et al., 2013</td>
</tr>
<tr>
<td>PCDH19 female pediatric epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Sample size</td>
<td>Target patients</td>
<td>Study design</td>
<td>Dosing tested and duration</td>
<td>Results</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>---------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>NCT02358538 (Phase II)</td>
<td>Female children aged 2–10 years with PCDH19 mutations and other rare genetic epilepsies with uncontrolled seizures and on a stable AED regimen</td>
<td>Multicenter, open-label, proof-of-concept</td>
<td>Ganaxolone 1,800mg/day or 63mg/kg/day for six months</td>
<td>Primary endpoint: Percentage change in seizure (focal dyscognitive or focal convulsive) frequency per 28 days relative to baseline.</td>
<td>Responder rate for at least one 28-day treatment period: 63% (five out of eight)</td>
<td>Biomedtracker; ClinicalTrials.gov</td>
</tr>
</tbody>
</table>

AED = anti-epileptic drug

Source: various (see above)
SWOT ANALYSIS

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Novel, first-in-class neurosteroid GABA_A-positive modulator</td>
<td>• Clinical trial data suggest weak anti-seizure effect</td>
</tr>
<tr>
<td>• Proof-of-concept study hints at efficacy in PCDH19 female epilepsy</td>
<td>• Clinical investigation in West syndrome and adult refractory partial-onset seizures failed to meet significance and was discontinued</td>
</tr>
<tr>
<td>• Demonstration of favorable tolerability</td>
<td>• Marinus Pharmaceuticals’ lack of commercialization and marketing capabilities</td>
</tr>
<tr>
<td>• Preclinical evidence for broad spectrum of activity in epilepsy</td>
<td>• High discontinuation rates mainly due adverse events</td>
</tr>
<tr>
<td>• Orphan drug designation for status epilepticus and PCDH19 pediatric epilepsy will expedite development</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Seek a licensing partnership with an established company in the CNS market</td>
<td>• Translation of the weak efficacy in partial-onset seizures to PCDH19 epilepsy and status epilepticus</td>
</tr>
<tr>
<td>• Demonstration of clinical benefit in niche populations such as catamenial epilepsy</td>
<td>• High brand loyalty impedes market penetration</td>
</tr>
<tr>
<td>• Continue development in the treatment of status epilepticus and PCDH19 epilepsy</td>
<td>• Investigation in non-epilepsy indications, including fragile X syndrome, could take resources away from developing the drug for epilepsy</td>
</tr>
<tr>
<td>• Initiate investigation in Japanese and EU epilepsy markets upon securing development and commercialization partner</td>
<td></td>
</tr>
</tbody>
</table>

CNS = central nervous system; PCDH19 = protocadherin 19

Source: Datamonitor Healthcare
CLINICAL AND COMMERCIAL ATTRACTIVENESS

The figures below depict Datamonitor Healthcare's drug assessment summary of ganaxolone for epilepsy. Keppra (levetiracetam; UCB) represents the comparator therapy for both marketed and pipeline epilepsy therapies.

Figure 2: Datamonitor Healthcare’s drug assessment summary for ganaxolone in epilepsy

Source: Datamonitor Healthcare
Ganaxolone’s failure to demonstrate efficacy in partial-onset seizures limits its commercial potential

In June 2016, Marinus Pharmaceuticals announced the discontinuation of further development of ganaxolone as a treatment for partial-onset seizures, after the company's Phase III trial only showed a small anticonvulsant effect (Marinus Pharmaceuticals, 2016a). The approximate 20% reduction in seizure frequency – and subsequent failure to meet the primary endpoint showing significance versus placebo – suggests that ganaxolone has a very modest and uncompetitive efficacy profile, which may also harm its further development and opportunity for other epilepsy subtypes. In addition, the discontinuation rate in the ganaxolone treatment arm (25%) was almost twice as high as that of the placebo arm (14%), which raises concerns about the drug’s tolerability (Marinus Pharmaceuticals, 2016a). Subsequently, Marinus Pharmaceuticals decided to discontinue the development of this program, indicating its plans to focus its efforts on niche epilepsy indications.

With an orphan indication lacking in approved therapies, ganaxolone may prove an attractive product for PCDH19 female epilepsy patients, should efficacy be established

Despite ganaxolone’s failure to demonstrate efficacy in adult partial-onset seizures, the drug was found to be safe, with the most common side effects reported being somnolence (23.5% ganaxolone versus 4.5% placebo), dizziness (19.6% versus 4.5%), and fatigue (11.7% versus 6.8%). As such, Marinus Pharmaceuticals plans to leverage the safety of its product and continue its development in orphan niche indications including PCDH19 female epilepsy (Marinus Pharmaceuticals, 2016a).
PCDH19 female epilepsy is an infantile-onset syndrome that is inheritable and affects female patients only. An X-linked mutation of the PCDH19 gene results in the expression of different and multiple seizure types in girls from as early as eight months old. In addition to exhibiting cluster seizures, some of these patients display cognitive delays, autism, and behavioral disturbances. This form of epilepsy currently lacks any approved therapies and affects approximately 15,000–30,000 females in the US (Marinus Pharmaceuticals, 2015d).

A recent study has provided a scientific rationale for the evaluation of ganaxolone in PCDH19 female epilepsy. The transcriptome study carried out on the primary skin fibroblast collected from PCDH19 and control subjects identified certain dysregulated genes otherwise associated with allopregnanolone production. This translated into lower levels of allopregnanolone in the blood of patients with the PCDH19 mutation, as confirmed by blood analysis. These findings suggest the role of neurosteroids in epileptogenesis and provided a scientific rationale for the evaluation of the synthetic analog of allopregnanolone in the treatment of PCDH19 female epilepsy patients (Tan et al., 2015). Given the urgent unmet need in treating this orphan disease and the supporting preclinical studies, the US Food and Drug Administration has granted ganaxolone orphan drug designation for the treatment of PCDH19 female pediatric epilepsy. Obtaining such a designation comes with many benefits. In addition to a seven-year market exclusivity period, the designation provides Marinus Pharmaceuticals with tax credits for clinical research costs, clinical research trial design assistance, a waiver of Prescription Drug User Fee Act costs, and the ability to apply for annual grant funding (Marinus Pharmaceuticals, 2015b). These factors will likely expedite ganaxolone’s development. Additionally, should ganaxolone’s efficacy be established in the treatment of PCDH19 female epilepsy, the drug would certainly become a first-line therapy in an indication that otherwise lacks appropriate therapies and would therefore have no foreseeable competition.

Lack of a licensing partner will hinder progress

Datamonitor Healthcare believes that Marinus Pharmaceuticals should also investigate ganaxolone in other epilepsy subtypes, as evidence from preclinical trials suggests that the drug has potential efficacy against generalized seizures, with a spectrum of activity similar to ethosuximide and valproate (Nohria and Giller, 2007). However, given that Marinus is also investigating ganaxolone as a potential treatment for fragile X syndrome, Datamonitor Healthcare predicts that without a licensing partner, development in further epilepsy indications will be hindered due to a lack of resources. Marinus Pharmaceuticals lacks the commercialization and marketing experience of other companies within the epilepsy market. As such, Datamonitor Healthcare recommends that the company should seek a commercialization partner with experience in the central nervous system market. Should ganaxolone prove to be a viable approach to managing orphan indications within epilepsy, this could help the company find a partner.

Bibliography


