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TABLE OF CONTENTS

5 EXECUTIVE SUMMARY

6 CLINICAL PIPELINE OVERVIEW

7 TARGET PRODUCT PROFILE

7 Comparator therapies

11 Target product profile versus current level of attainment

14 Bibliography

15 CLINICAL TRIAL DESIGN IN DEPRESSION

15 Clinical trials

24 Future developments in clinical trial design

28 Bibliography

30 INNOVATIVE EARLY-STAGE APPROACHES

31 Glutamate receptor modulation

33 Targeting neuropeptides for depression

36 Bibliography

38 THE FUTURE OF TREATMENT IN DEPRESSION

38 Specific targeting of treatment-resistant patients

41 Biomarkers for depression

45 Bibliography

48 OTHER KEY DRUGS IN DEVELOPMENT FOR DEPRESSION

48 Amitifadine (EB-1010; Euthymics Bioscience)

49 Cariprazine (RGH-118; Forest/Gedeon Richter/Mitsubishi Tanabe)

49 Filorexant (MK-6096; Merck & Co.)

51 GLYX-13 (Naurex)

51 Drug profile

52 Clinical trials

52 Latuda (lurasidone; Dainippon Sumitomo/Takeda)

54 Lu AA24530 (tedatioxetine; Lundbeck/Takeda)

56 PNB-01 (pipamperone/citalopram; Pharma Neuro Boost)

57 RG7090 (Roche)

59 Bibliography

63 LATE STAGE DRUGS

63 ALKS 5461 : Depression

71 brexipiprazole : Depression

81 APPENDIX

81 Contributing experts
LIST OF FIGURES

38 Figure 1: Potential timeline for future depression therapies
39 Figure 2: Segmentation of depression patients by subtype in the US, Japan, and five major EU markets, 2013
44 Figure 3: BRITE-MD study of the Antidepressant Treatment Response Index as a functional biomarker for depression
65 Figure 4: ALKS 5461 (buprenorphine/samidorphan; Alkermes) SWOT analysis for depression
66 Figure 5: Datamonitor Healthcare’s drug assessment summary for ALKS 5461 (buprenorphine/samidorphan) in depression
67 Figure 6: Datamonitor Healthcare’s drug assessment summary for ALKS 5461 (buprenorphine/samidorphan) in depression
76 Figure 7: Brexpiprazole (OPC-34712; Otsuka) SWOT analysis for depression
77 Figure 8: Datamonitor Healthcare’s drug assessment summary for brexpiprazole in depression
78 Figure 9: Datamonitor Healthcare’s drug assessment summary for brexpiprazole in depression

LIST OF TABLES

6 Table 1: Drugs currently in late-stage development for depression
7 Table 2: Lexapro (escitalopram; Forest/Lundbeck) – drug profile in depression
9 Table 3: Defining the gold standard for depression: key clinical trial results for Lexapro
12 Table 4: Target product profile in major depressive disorder
16 Table 5: Comparison between the HAM-D and MADRS rating scales for depression
19 Table 6: Typical Phase III clinical trial design in major depressive disorder
22 Table 7: Key facts: Lexapro (escitalopram; Forest/Lundbeck) versus Cymbalta (duloxetine; Eli Lilly) comparator trial in major depressive disorder
24 Table 8: Key facts: Symbyax (fluoxetine and olanzapine; Eli Lilly) pivotal Phase III clinical trial
26 Table 9: Key facts: Abilify (aripiprazole; Bristol-Myers Squibb/Otsuka) pivotal Phase III clinical trial
27 Table 10: Key facts: Seroquel XR (quetiapine fumarate extended release; AstraZeneca) Phase III clinical trial
30 Table 11: Most promising innovative therapeutic approaches in depression
50 Table 12: Key facts: Phase II trial of filorexant (MK-6096; Merck & Co.) in major depressive disorder
53 Table 13: Key facts: Phase III trial of Latuda in major depressive disorder with mixed features
55 Table 14: Key facts: Phase II trial of Lu AA24530 (tedatioxetine; Lundbeck/Takeda) in major depressive disorder
58 Table 15: Key facts: Phase II trial of RG7090 in treatment-resistant depression
63 Table 16: ALKS 5461 (buprenorphine/samidorphan; Alkermes) – drug profile in depression
71 Table 17: Brexpiprazole (OPC-34712; Otsuka/Lundbeck) – drug profile in depression
74 Table 18: Pivotal clinical program for brexpiprazole in major depressive disorder
There have been a large number of clinical trials examining Lexapro for use in patients with depression. A fixed-dose study using citalopram as a comparator demonstrated that not only did Lexapro display statistically significant improvement over placebo on key efficacy measures; evidence was also provided for a benefit over citalopram (Burke et al., 2002). Lexapro has also been demonstrated to be a safe and well-tolerated treatment for depression, with low dose Lexapro (10mg/day) associated with a similar incidence of treatment-emergent adverse events and discontinuation (Lundbeck, 2002). Furthermore, post-marketing studies have examined the benefit of
### Table 10: Key facts: Seroquel XR (quetiapine fumarate extended release; AstraZeneca) Phase III clinical trial

<table>
<thead>
<tr>
<th>Comparing Quetiapine XR Monotherapy and Augmentation with Lithium Augmentation in TRD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study title</strong></td>
</tr>
<tr>
<td><strong>Objective of trial</strong></td>
</tr>
<tr>
<td><strong>Trial design</strong></td>
</tr>
<tr>
<td><strong>Primary outcome measures</strong></td>
</tr>
<tr>
<td><strong>Key secondary outcome measures</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; CGI-S = Clinical Global Impression – Severity; MADRS = Montgomery-Asberg Depression Rating Scale; SSRI = selective serotonin reuptake inhibitor; TRD = treatment-resistant depression

Source: ClinicalTrials.gov (NCT00789854)

### Bibliography

**JOURNAL PAPERS**

THE FUTURE OF TREATMENT IN DEPRESSION

The antidepressants market has reached a mature state, with generic versions of popular selective serotonin reuptake inhibitors (SSRIs) well-established at first line. The end of Lexapro’s (escitalopram; Forest/Lundbeck) patent life will herald the end of an extremely productive era for the big players in depression, beginning in the 1990s when relatively undifferentiated SSRIs could be marketed to all patients and sold at prices unhindered by the presence of equally effective generic antidepressants. Increasingly, drug developers will need to look at niche populations and address specific unmet needs in order to gain traction in the depression market.

The figure below presents Datamonitor Healthcare’s prediction of the future depression treatment landscape with timelines of market-shifting events.

![Figure 1: Potential timeline for future depression therapies](source: Datamonitor Healthcare)

**Specific targeting of treatment-resistant patients**

**A LABEL FOR TREATMENT-RESISTANT DEPRESSION WILL BYPASS COMPETITION WITH GENERIC FIRST-LINE ANTIDEPRESSANTS**

Datamonitor Healthcare believes that the saturation of the first- and second-line antidepressant therapy market with generic selective serotonin reuptake inhibitors (SSRIs) such as citalopram, sertraline, fluoxetine, and paroxetine will increasingly force drug developers to specifically target later lines of therapy, either as a monotherapy or more likely as an adjunct to existing SSRIs. Gaining regulatory approval as an adjunctive therapy in a difficult-to-treat patient subpopulation would provide the platform for entry to the market, bypassing competition from cheap and efficacious generic formulations. This is already the case for trials of prospective antiepileptic drugs, where due to ethical reasons, it is not appropriate to randomize treatment-refractory patients in clinical trials to
RG7090 until beyond 2014 (Roche, 2012).

An increasing body of evidence indicates that glutamate has a role in the pathophysiology of depression (Palucha, 2006). The mGluR5 is highly expressed in regions of the brain that are implicated in mood disorders (Shigemoto et al., 1993). Furthermore, mGluR5-knockout mice performed significantly better than wild-type mice in the forced swim test – a rodent behavioral model for depression – with the mutant mice displaying no effect to the administration of a negative allosteric mGluR5 modulator (Li et al., 2006). The knockout mice were still responsive to the tricyclic antidepressant imipramine, demonstrating that a distinct pathway is involved in the antidepressant effect of mGluR5 modulation.

While Roche is the sole company looking specifically at mGluR5 antagonists, there is considerable pharmaceutical interest in the overall glutamate system and depression. The mGluR2 and mGluR3 subtypes are also attracting attention as drug targets, as well as NMDA and AMPA receptors. Interestingly, all of the glutamate receptor modulators that are in Phase II clinical trials are specifically targeting the treatment-resistant depression subpopulation.

**CLINICAL TRIALS**

Roche has completed an exploratory 34-patient Phase II trial to investigate the safety and tolerability of RG7090 in treatment-resistant depression over the course of 10 days (ClinicalTrials.gov identifier: NCT00809562). The results of this trial have not been made publicly available, although Roche has since initiated and completed a larger 300-patient trial (MARIGOLD), so the initial study can be presumed to have shown adequate safety.

The design of the second Phase II trial is shown in the table below. Please note that RG7090 is referred to as RO4917523 in the trial information.