New Schizophrenia Treatments Address Unmet Clinical Needs

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Schizophrenia is a chronic brain disorder primarily characterized by delusions, hallucinations, difficulty with thinking and concentration, and lack of motivation. The disorder affects approximately 1% of the U.S. population.[1] The precise cause of schizophrenia is unknown, but some investigators have suggested that it may begin *in utero*.[2,3] Genetic, environmental, and social factors have also been implicated.[4,5]

Although there is no cure for schizophrenia,[1] numerous drugs are available for initial and maintenance therapy, with the goal of controlling symptoms.[6] According to the American Psychiatric Association, second-generation (atypical) antipsychotics—with the exception of clozapine—are the agents of choice for the first-line treatment of schizophrenia.[7] Clozapine is not recommended because of its risk for causing agranulocytosis or seizures.[2,8] All of the atypical antipsychotic drugs offer comparable efficacy.[9,10] After patients have recovered from their acute psychotic episode, maintenance therapy is initiated.[11]

Most schizophrenia patients (approximately 80% to 90%) experience a relapse during the course of their illness.[12] Breakthrough psychotic episodes may result from nonadherence to maintenance therapy, persistent substance use, poorer premorbid adjustment, or stressful life events.[13] Long-acting injectable antipsychotics are commonly used to prevent relapse.[14] In addition, adjunctive psychosocial interventions—including family psychosocial education, social skills training, and cognitive behavioral therapy—have been shown to prevent relapse and to improve medication adherence.[7,15]

Approximately 10% to 30% of schizophrenic patients are treatment resistant.[7] The optimal management of these patients may require switching to the atypical antipsychotic clozapine or augmenting current therapy with other approaches.[16,17] Augmentation treatments include the use of electroconvulsive therapy or repetitive transcranial magnetic stimulation.[18,19]

Table 1 lists the leading schizophrenia treatments in the United States.[6]

Analysts have identified five unmet needs in the schizophrenia marketplace. They include:[6]

- Drugs that enhance cognition
- Drugs that treat negative symptoms (such as lethargy, apathy, and social withdrawal)
- Drugs that provide improved options for treatment-resistant patients
- Drugs with enhanced safety profiles
- Drugs that increase compliance

With these needs in mind, pharmaceutical companies are working to develop several novel schizophrenia drugs (Table 2). These investigational therapies are discussed below.

ALKS 3831 (Alkermes) is a fixed-dose combination of samidorphan, a mu-opioid receptor antagonist, and the atypical antipsychotic drug olanzapine (generic Zyprexa).[6] The combination treatment uses the action of samidorphan to reduce the weight gain and metabolic adverse events associated with olanzapine while maintaining olanzapine's antipsychotic efficacy.[6]

ALKS 3831 was evaluated in a 12-week, phase 2, randomized, double-blind, active-controlled, dose-ranging study involving 300 adults with schizophrenia. Alkermes reported top-line results from this trial in January 2015. ALKS 3831 achieved the study's primary efficacy endpoint, demonstrating equivalence to olanzapine in the reduction from baseline in Positive and Negative Syndrome Scale (PANSS) total scores. ALKS 3831 also met the study's principal secondary endpoints, demonstrating a 37% lower mean weight gain compared with olanzapine at week 12 in the full study population ($P = 0.006$) and a 51% lower mean weight gain compared with olanzapine at week 12 in a subset of patients who gained weight in the one-week olanzapine lead-in ($P < 0.001$).[20]

Based on these positive findings, Alkermes has moved ALKS 3831 into a phase 3 clinical development program consisting of two trials: ENLIGHTEN-1 and ENLIGHTEN-2. In the first study, ALKS 3831 is being compared with olanzapine alone and placebo in an estimated 390 patients with schizophrenia. The primary endpoint is the change in the PANSS score after four weeks of treatment. The study began in December 2015 and has an anticipated completion date of April 2018.[21] The second trial is evaluating weight gain during treatment with ALKS 3831 compared with olanzapine in adults with schizophrenia. The study has two primary endpoints: the percent change from baseline in body weight at 24 weeks and the proportion of patients with 10% or greater weight gain at the same time point. The study was initiated in February 2016, with a projected completion date of March 2018.[22]

If ALKS 3831 is approved by the Food and Drug Administration (FDA), it is expected to be launched in the U.S. in the third quarter of 2019.[6]

AVN-211 (Avineuro Pharmaceuticals) is an oral, small-molecule antagonist of the 5-hydroxytryptamine 6 (5-HT_6) family of serotonin receptors that has received attention as a potential adjunctive treatment for the cognitive impairments associated with schizophrenia. There are no marketed drugs with this indication.[6]

In 2015, however, AVN-211 failed to demonstrate statistically significant results in a phase 2 pilot study, which evaluated the efficacy of AVN-211 in amplifying the effects of antipsychotic drugs in 80 patients with schizophrenia in incomplete remission receiving stable antipsychotic therapy. AVN-211 was not significantly different from placebo on the study's primary efficacy endpoint.[23]

Moreover, as a drug discovery and development company, Avineuro may lack the sales and marketing expertise required for a successful launch of AVN-211. Therefore, the company may need to attract a partner or forge a licensing agreement to maximize the drug's com-

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Table 1 Leading Atypical Antipsychotics for the Treatment of Schizophrenia Patients in the U.S.[6]

Drug *Developer*	Brand	Primary Indication	U.S. Launch	Primary Patent or Exclusivity Expiry
Aripiprazole *Otsuka*	Abilify	Schizophrenia in adults and adolescents (ages 13–17 years); agitation associated with schizophrenia	2002	April 2015
	Abilify Maintena	Schizophrenia in adults	2013	October 2024
Aripiprazole lauroxil *Alkermes*	Aristada	Schizophrenia in adults	2015	October 2033
Asenapine *Organon/Merck*	Saphris	Schizophrenia in adults	2009	October 2026
Brexipiprazole *Otsuka/Lundbeck*	Rexulti	Schizophrenia in adults	2015	February 2027
Cariprazine *Allergan*	Vraylar	Schizophrenia	2016	December 2028
Clozapine *Novartis*	Clozaril	Treatment-resistant schizophrenia; reduction in risk of recurrent suicidal behavior in schizophrenia and schizoaffective disorder	1989	Numerous generics
Iloperidone *Vanda*	Fanapt	Schizophrenia in adults	2010	November 2016
Lurasidone *Dainippon Sumitomo*	Latuda	Schizophrenia in adults	2011	July 2018
Olanzapine *Lilly*	Zyprexa	Schizophrenia in adults and adolescents (ages 13–17 years); agitation associated with schizophrenia	1996	October 2011
Olanzapine pamoate *Lilly*	Zyprexa Relprevv	Schizophrenia in adults	2009	September 2018
Paliperidone *Janssen*	Invega	Schizophrenia in adults and adolescents (ages 12–17 years)	2006	April 2012
Paliperidone palmitate *Janssen*	Invega Sustenna	Schizophrenia in adults	2009	May 2019
	Invega Trinza	Schizophrenia in adults after receiving Invega Sustenna for four months	2015	May 2018
Quetiapine *AstraZeneca/Astellas*	Seroquel	Schizophrenia in adults and adolescents (ages 13–17 years)	1997	March 2012
	Seroquel XR	Schizophrenia in adults and adolescents (ages 13–17 years)	2007	November 2017
Risperidone *Janssen*	Risperdal	Schizophrenia in adults and adolescents (ages 13–17 years)	1994	June 2008
	Risperdal Consta	Schizophrenia in adults	2003	2023
Ziprasidone *Pfizer*	Geodon	Schizophrenia in adults; agitation associated with schizophrenia	2001	March 2012

mercial potential. At the present time, the future of AVN-211 remains uncertain.[6]

ITI-007 (Intra-Cellular Therapies) is a selective 5-HT_{2A} receptor antagonist that is in phase 3 clinical development for the treatment of patients with acute or residual schizophrenia.[6] At increased doses, the drug may provide additional benefits, including modest dopamine receptor modulation and modest inhibition of serotonin transporters.[24]

A phase 3 study of ITI-007 in schizophrenia patients was completed in September 2015, with positive results. Once-daily ITI-007 60 mg met the study's primary endpoint, demonstrating antipsychotic efficacy with statistically significant superiority over placebo at week 4 (the study endpoint), as measured by the change from baseline in PANSS total score (P = 0.022). Moreover, ITI-007 60 mg showed significant antipsychotic efficacy as early as week 1, which was maintained throughout the study.[25]

However, in a second phase 3 trial of ITI-007 in schizophrenia patients, the drug did not differ significantly from placebo in its effect on the primary endpoint (the change from baseline in the PANSS score), whereas the active control, risperidone, did separate from placebo. Intra-Cellular Therapies blamed ITI-007's poor showing on an unusually high placebo response rate (even though this response did not affect risperidone).[26]

If ITI-007 gains FDA approval, analysts anticipate that it will be launched in the U.S. in the first half of 2018.[6]

Lu AF35700 (Lundbeck) is an antagonist of the D_1, 5-HT_{2A}, and 5-HT_6 receptors. Based on its pharmacological profile, the drug is expected to reduce the occurrence of adverse events associated with the use of several antipsychotics, including extrapyramidal symptoms, elevated prolactin levels, dysphoria/anhedonia, and depressed mood.[6,27]

Two doses of Lu AF35700 (10 mg and

Table 2 Promising Compounds in Clinical Development for the Treatment of Schizophrenia in Adults[6]

Drug *Developer*	Description	Targeted Indication(s)	Expected Pricing Strategy	Anticipated U.S. Launch Date
Atypical Antipsychotics				
ALKS 3831 *Alkermes*	Fixed-dose combination of mu-opioid receptor antagonist (samidorphan) and atypical antipsychotic (olanzapine)	Schizophrenia (acute exacerbations or stable disease)	Priced at premium to olanzapine (Zyprexa, Lilly)	Third quarter of 2019
AVN-211 *Avineuro Pharmaceuticals*	5-HT_6 receptor antagonist	Cognitive impairments associated with schizophrenia	Undetermined	Undetermined
ITI-007 *Intra-Cellular Therapies*	5-HT_{2A} receptor antagonist	Acute and residual schizophrenia	Priced at premium to currently marketed oral antipsychotics	First half of 2018
Lu AF35700 *Lundbeck*	D_1, 5-HT_{2A}, and 5-HT_6 receptor antagonist	Treatment-resistant schizophrenia	Undetermined	Undetermined
MIN-101 *Minerva Neurosciences*	5-HT_{2A} and sigma-2 receptor antagonist	Schizophrenia	Priced at premium to currently marketed oral antipsychotics	2019
RBP-7000 *Indivior*	Sustained-release risperidone	Schizophrenia (acute or maintenance treatment)	Priced at premium to Risperdal Consta (Janssen)	Fourth quarter of 2017
Risperidone implant *Braeburn Pharmaceuticals*	Six-month, nonbiodegradable, drug-eluting stent	Schizophrenia (maintenance treatment)	Priced at 15% premium to annual cost of therapy with Risperdal Consta	Second quarter of 2018
Risperidone ISM *Rovi Pharmaceutical Laboratories*	Once-monthly IM formulation based on ISM delivery system	Schizophrenia or schizoaffective disorder	Priced at premium to Risperdal Consta	Fourth quarter of 2019
Hyperammonemia Agent				
Sodium benzoate (NaBen) *SyneuRx International (Taiwan) Corp.*	D-amino acid oxidase inhibitor	• Pediatric schizophrenia • Refractory schizophrenia (in combination with clozapine) • Adjunctive therapy for schizophrenia in adults	Undetermined	Undetermined

5-HT = 5-hydroxytryptamine; IM = intramuscular; ISM = *in situ* microparticles.

20 mg) are being evaluated in a phase 3 trial involving an estimated 964 adults with treatment-resistant schizophrenia. The primary endpoint is the change from baseline to study week 10 in the PANSS total score. The study began in March 2016, with an estimated completion date of May 2018.[28,29]

MIN-101 (Minerva Neurosciences) is a first-in-class 5-HT_{2A} and sigma-2 receptor antagonist. These receptors play a role in regulating mood, sleep, cognition, and anxiety. By blocking 5-HT_{2A} receptors, MIN-101 is believed to minimize the hallucinations, delusions, agitation, and thought and movement disorders associated with schizophrenia. Moreover, antagonism of sigma-2 receptors modulates dopamine, a neurotransmitter that has been implicated in the pathophysiology of schizophrenia. It also increases intracellular calcium levels in brain neurons, which can result in enhanced memory.[30]

Positive results were reported from a 12-week, phase 2b, prospective, randomized, double-blind, placebo-controlled, parallel-group trial that evaluated MIN-101 versus placebo in 244 patients with negative symptoms of schizophrenia (i.e., disruptions to normal emotions and behaviors). The study achieved its primary endpoint, demonstrating a statistically significant benefit of MIN-101 over placebo in improving negative symptoms, as measured by the PANSS. The effect was observed for both the 32-mg and 64-mg doses of MIN-101 ($P \leq 0.022$ and $P \leq 0.003$, respectively).[31]

Phase 3 testing of MIN-101 is expected to begin in 2017.[32] If the drug is approved, its anticipated launch date is 2019.[6]

RBP-7000 (Indivior) is a monthly sustained-release formulation of risperidone, one of the most frequently prescribed atypical antipsychotics for schizophrenia.[6] The product consists of a two-syringe system in which the contents are mixed immediately before administration. One syringe contains a delivery system (Atrigel), and the other contains powdered risperidone.[33] The mixture is injected subcutaneously as a liquid into the patient's abdomen, where it subsequently solidifies, resulting in the prolonged release of risperidone for one month before it eventually biodegrades.[34]

In May 2015, Indivior reported positive results from a pivotal phase 3 study of RBP-7000 (90 mg and 120 mg once monthly) in patients with schizophrenia. The study met its primary endpoint of providing statistically significant reductions in the symptoms of acute schizophrenia, as determined by PANSS scores, compared with placebo during the eight-week

treatment period. RBP-7000 also met the key secondary endpoint with significant improvements in the Clinical Global Impression–Severity scale compared with placebo during the eight-week treatment period, as indicated by the change from baseline to the end of treatment.[33]

Indivior subsequently announced that it was weighing the options for the final stages of clinical development and commercialization of RBP-7000. These options included potential partnerships, outlicensing or outright sale of the product, and maintaining ownership of the product.[34,35]

Analysts anticipate that RBP-7000 will be launched in the U.S. in the fourth quarter of 2017, with an indication for acute and maintenance treatment of patients with schizophrenia. It is expected, however, to meet strong competition from generic risperidone.[6]

Braeburn Pharmaceuticals is developing an implantable six-month formulation of risperidone, which it acquired from Endo Pharmaceuticals. The nonbiodegradable, drug-eluting implant is designed to deliver risperidone for maintenance treatment of schizophrenia patients.[6,36]

A 48-week, phase 3, open-label study is evaluating the safety and tolerability of risperidone implants as maintenance therapy in 145 adults (18 to 70 years of age) with schizophrenia. The study's primary outcome measure is the number of participants with treatment-related adverse events. The study began in April 2016 and is expected to be completed in November 2017.[37]

As of December 2016, no efficacy data for the risperidone implant have been published. If the product is approved, analysts expect a 2018 launch.[6]

Risperidone is also being developed in the form of *in situ* microparticles (ISM) by a Spanish company, Rovi Pharmaceutical Laboratories. Risperidone ISM consists of two syringes—one containing a polymer and the active ingredient in a solid state, and the other containing the solvent needed for reconstitution—for once-monthly intramuscular administration.[38]

Rovi completed a phase 2 pharmacokinetics and tolerability study of risperidone ISM in schizophrenia patients in March 2015[39] and presented the results to the 24th European Congress of Psychiatry in March 2016.[40] Shortly afterward, Rovi submitted the PRISMA-2 data, along with findings from previous studies, to the FDA in order to request guidance on the design of a phase 3 trial of risperidone ISM. The company predicted that recruitment for such a study would be under way by the third quarter of 2016.[40]

If approved, risperidone ISM is expected to be launched in the U.S. in the fourth quarter of 2019 for the treatment of patients with schizophrenia or schizoaffective disorder.[6]

NaBen (sodium benzoate, SyneuRx International [Taiwan] Corp.) is a D-amino acid oxidase inhibitor under clinical development as a schizophrenia treatment.[6] It was granted orphan drug status for the treatment of schizophrenia patients with refractory disease in combination with clozapine in December 2011 and for the treatment of schizophrenia in pediatric patients in July 2012.[41] In December 2014, NaBen also won a breakthrough therapy designation as an adjunctive treatment for schizophrenia in adults.[42]

A phase 2, randomized, double-blind, placebo-controlled trial was conducted in Taiwan to determine the clinical and cognitive efficacy of add-on treatment with sodium benzoate in patients with schizophrenia who had been stabilized with antipsychotic medications for at least three months. Fifty-two patients received six weeks of add-on treatment with 1 g daily of sodium benzoate or placebo. Sodium benzoate was associated with a 21% improvement in the PANSS total score compared with placebo. Significantly greater improvements were also observed in Scales for the Assessment of Negative Symptoms–20 items, the Global Assessment of Function, the Quality of Life Scale, and the Clinical Global Impression in patients receiving add-on sodium benzoate treatment compared with placebo treatment.[43]

SyneuRx filed a proposed phase 2b/3 study of sodium benzoate with the National Institutes of Health in September 2014, but as of December 2016, no subjects have been recruited. The multicenter, prospective, randomized, placebo-controlled, sequential parallel comparison design trial is expected to enroll an estimated 240 adults with schizophrenia. The study will consist of a 19-week double-blind phase followed by a 26-week open-label extension phase.[44]

In summary, several products are being developed to address the significant unmet needs that exist in the schizophrenia marketplace. For example, three potential treatments—ITI-007 (Intra-Cellular Therapies), MIN-101 (Minerva Neurosciences), and NaBen (SyneuRx)—are aimed at managing the negative symptoms of the disease. In addition, AVN-211 (Avineuro Pharmaceuticals) is in late-stage development as a treatment for the cognition impairments associated with schizophrenia, and Lu AF35700 (Lundbeck) addresses treatment resistance in schizophrenia patients. Finally, three formulations of risperidone—risperidone implant (Braeburn Pharmaceuticals), risperidone ISM (Rovi), and RBP-7000 (Indivior)—are expected to offer improved safety profiles.[6]

REFERENCES

1. American Psychiatric Association. What is schizophrenia? July 2015. Available at: www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia. Accessed November 1, 2016.
2. Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach,* 9th ed. New York, New York: McGraw-Hill; 2014:1019–1046.
3. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1999;20:201–225.
4. McDonald C, Murphy KC. The new genetics of schizophrenia. *Psychiatr Clin North Am* 2003;26:41–63.
5. Lavretsky H. History of schizophrenia as a psychiatric disorder. In: Mueser KT, Jeste DV, eds. *Clinical Handbook of Schizophrenia*. New York, New York: Guilford Press; 2008:3–12.
6. Michaelidis C, Markwick R, Robbins R. *Schizophrenia—Global Drug Forecast and Market Analysis to 2025*. New York, New York: GlobalData; November 2016.
7. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia: second edition. *Am J Psychiatry* 2004;161(suppl 2):S1–S56.
8. Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. *Can J Psychiatry* 2007;52:457–463.
9. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010;36:71–93.
10. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;373:31–41.

11. Stroup TS, Marder S. Pharmacotherapy for schizophrenia: acute and maintenance phase treatment. *UpToDate*. July 24, 2015. Available at: www.uptodate.com/contents/pharmacotherapy-for-schizophrenia-acute-and-maintenance-phase-treatment. Accessed November 2, 2016.
12. Emsley R, Chiliza B, Asmal L, Harvey BH. The nature of relapse in schizophrenia. *BMC Psychiatry* 2013;13:50. doi: 10.1186/1471-244X-13-50.
13. Alvarez-Jimenez M, Priede A, Hetrick SE, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Schizophr Res* 2012;139:116–128.
14. Lauriello J, Campbell AR. Pharmacotherapy for schizophrenia: long-acting injectable antipsychotic drugs. *UpToDate*. March 1, 2016. Available at: www.uptodate.com/contents/pharmacotherapy-for-schizophrenia-long-acting-injectable-antipsychotic-drugs. Accessed November 15, 2016.
15. Bustillo J, Weil E. Psychosocial interventions for schizophrenia. *UpToDate*. October 13, 2016. Available at: www.uptodate.com/contents/psychosocial-interventions-for-schizophrenia. Accessed November 15, 2016.
16. Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev* 2009 Jan 21;(1):CD000059. doi: 10.1002/14651858.CD000059.pub2.
17. Souza JS, Kayo M, Tassell I, et al. Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses. *CNS Spectr* 2013;182:82–89.
18. Dlabac-de Lange JJ, Knegtering R, Aleman A. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. *J Clin Psychiatry* 2010;71:411–418.
19. Kane J, Kishimoto T, Correll CU. Treatment-resistant schizophrenia. June 7, 2016. *UpToDate*. Available at: www.uptodate.com/contents/treatment-resistant-schizophrenia. Accessed November 29, 2016.
20. Alkermes, Inc. Alkermes announces positive results of phase 2 clinical trial of ALKS 3831 in schizophrenia. January 7, 2015. Available at: http://investor.alkermes.com/mobile.view?c=92211&v=203&d=1&id=2004543. Accessed November 1, 2016.
21. ClinicalTrials.gov. A study of ALKS 3831 in adults with acute exacerbation of schizophrenia (the ENLIGHTEN-1 study). NCT02634346. October 24, 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02634346. Accessed November 2, 2016.
22. ClinicalTrials.gov. A study of ALKS 3831 in adults with schizophrenia (the ENLIGHTEN-2 study). NCT02694328. September 16, 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02694328. Accessed November 2, 2016.
23. Avineuro Pharmaceuticals. Avineuro completed phase II clinical study of AVN-211. July 16, 2015. Available at: www.avineuro.com/avineuro-completed-phase-ii-clinical-study-of-avn-211-a-selective-5-ht6-receptor-antagonist. Accessed November 3, 2016.
24. Intra-Cellular Therapies. ITI-007. 2014. Available at: www.intracellulartherapies.com/products-technology/iti-007.html. Accessed November 4, 2016.
25. Intra-Cellular Therapies. Intra-Cellular Therapies announces positive top-line results from the first phase trial of ITI-007 in patients with schizophrenia and confirms the unique pharmacology of ITI-007 in a separate positron emission tomography study. September 16, 2015. Available at: http://ir.intracellulartherapies.com/releasedetail.cfm?ReleaseID=931821. Accessed November 4, 2016.
26. Intra-Cellular Therapies. Intra-Cellular Therapies announces top-line results from the second phase trial of ITI-007 in patients with schizophrenia (Stud 032). September 28, 2016. Available at http://ir.intracellulartherapies.com/releasedetail.cfm?ReleaseID=991333. Accessed November 4, 2016.
27. Lundbeck. Pipeline: Lu AF35700. Available at: http://investor.lundbeck.com/pipeline.cfm. Accessed November 4, 2016.
28. ClinicalTrials.gov. Effect of Lu AF35700 in patients with treatment-resistant schizophrenia (DayBreak). NCT02717195. April 11, 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02717195. Accessed November 4, 2016.
29. Lundbeck. Lundbeck starts clinical phase III program with Lu AF35700 in patients with treatment-resistant schizophrenia. March 11, 2016. Available at: http://investor.lundbeck.com/releasedetail.cfm?releaseid=960101. Accessed November 4, 2016.
30. Minerva Neurosciences. MIN-101. Available at: www.minervaneurosciences.com/innovation-pipeline/min-101. Accessed November 4, 2016.
31. Minerva Neurosciences. Minerva Neurosciences announces positive results from phase IIb trial of MIN-101 monotherapy in schizophrenia. May 26, 2016. Available at: http://ir.minervaneurosciences.com/releasedetail.cfm?releaseid=972955. Accessed November 7, 2016.
32. Minerva Neurosciences. Minerva Neurosciences provides update on MIN-101 and MIN-117 clinical programs. September 26, 2016. Available at: http://ir.minervaneurosciences.com/releasedetail.cfm?releaseid=990851. Accessed November 7, 2016.
33. Indivior. Indivior PLC announces top-line results from pivotal phase 3 trial of RBP-7000 in schizophrenia. May 5, 2015. Available at: www.indivior.com/investor-news/indivior-plc-announces-positive-top-line-results-from-pivotal-phase-3-trial-of-rbp-7000-in-schizophrenia. Accessed November 8, 2016.
34. Indivior. Annual Report 2015. Available at: www.indivior.com/wp-content/uploads/2016/04/Indivior-Annual-Report-2015.pdf. Accessed November 8, 2016.
35. Indivior. Full Year Results 2015. Available at: www.indivior.com/wp-content/uploads/2016/02/Indivior-FY-2015-Results-Presentation.pdf. Accessed November 8, 2016.
36. Braeburn Pharmaceuticals. Braeburn Pharmaceuticals expands pipeline to include two schizophrenia treatments. May 1, 2015. Available at: https://braeburnpharmaceuticals.com/braeburn-pharmaceuticals-expands-pipeline-to-include-two-schizophrenia-treatments. Accessed November 15, 2016.
37. ClinicalTrials.gov. Safety and tolerability of risperidone implants. NCT02773576. October 7, 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02773576. Accessed November 15, 2016.
38. Laboratorios Farmaceuticos Rovi. Rovi will present positive results of risperidone ISM and bemiparin at the 12th EACPT Congress. June 26, 2015. Available at: www.rovi.es/ficheros/notas/ingles/Nota_de_Prensa_12th_EACPT_En.pdf. Accessed November 15, 2016.
39. ClinicalTrials.gov. Pharmacokinetics and tolerability study of risperidone ISM in schizophrenia (PRISMAS-2). NCT02086786. May 4, 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02086786. Accessed November 22, 2016.
40. Laboratorios Farmaceuticos Rovi. *First Quarter 2016 Results*. April 27, 2016. Available at: www.rovi.es/ficheros/notas/ingles/185i.pdf. Accessed November 22, 2016.
41. Health Resources and Services Administration, Department of Health and Human Services. Orphan drug designations and approvals list as of 12-01-2014. Available at: www.hrsa.gov/opa/programrequirements/orphandrugexclusion/janmar2015list.pdf. Accessed November 22, 2016.
42. Amarex Clinical Research. Amarex and SyneuRx announce FDA approval of breakthrough designation for schizophrenia treatment. December 10, 2014. Available at: www.amarexcro.com/news/10December2014.html. Accessed November 22, 2016.
43. Lane H-Y, Lin C-H, Green MF, et al. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. *JAMA Psychiatry* 2013;70:1267–1275.
44. ClinicalTrials.gov. Study to evaluate safety and efficacy of NaBen as add-on treatment for negative symptoms of schizophrenia in adults. NCT02261519. November 16, 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02261519. Accessed November 28, 2016. ■