**Introduction**

Schizophrenia is a complex and disabling mental disorder that is characterized by a range of symptoms and considerable psychosocial disability [1055772], [1055773]. The disorder is observed in all cultures, and has a global lifetime prevalence of approximately 1%, although some variability exists across countries [1049139], [1055774]. The typical age of onset of schizophrenia is in late adolescence or early adulthood (age 15 to 25 years), and the vast majority of patients have symptoms that persist throughout their adult life [1055773]. The symptoms of schizophrenia include a range of ‘positive symptoms’, which are characterized primarily by reality distortions, such as delusions and hallucinations [1055772]. Patients with schizophrenia also experience ‘negative symptoms’, which include a substantial reduction in motivation, drive and the capacity to feel pleasure [1055772]. Patients may also experience substantial abnormalities of cognition and disturbance of mood [1055772]. These symptoms are usually assessed in a research context through the use of standardized clinical rating scales and interview-based instruments, such as the Positive and Negative Syndrome Scale (PANSS) [447897]. The outcome of schizophrenia varies considerably: outcome is often poor with patients experiencing long-term psychosocial disability, but subgroups of patients with schizophrenia have extended periods of recovery [1055778]. In 2004, the WHO reported schizophrenia to be the fifth leading cause of disability among males and the sixth among females worldwide [590514].

**Treatments for schizophrenia principally comprise a range of antipsychotic medications that act primarily through an antagonism of monoamine receptors in the brain, mainly involving the dopamine D<sub>2</sub> receptor [1049140]. The first generation of antipsychotic medications, commonly referred to as typical antipsychotics, were all potent blockers of the D<sub>2</sub> receptor [1055783]. These agents (eg, haloperidol, chlorpromazine, perphenazine and fluphenazine) produce **
high rates of motor side effects, including Parkinsonism and tardive dyskinesia; for example, up to 40% of patients receiving haloperidol experience Parkinsonian side effects [1055784]. The second-generation medications (eg, isoperidone, olanzapine, quetiapine, risperidone and clozapine), referred to as atypical antipsychotics, have a more diverse range of actions. All of these drugs exert some degree of antagonism on the D₂ receptor, although the binding potentials (particularly the rate of dissociation from the receptor) vary considerably (K_d = 0.025 to 155 nM) [407898], [425505]. Most weakly bound drugs (eg, quetiapine) have a markedly reduced rate of motor side effects [407898]. Most atypical antipsychotics also bind to other receptors, such as the serotonin 5-HT₂A receptor and histamine receptors, although these effects may not influence efficacy [1055788], [1055790]. However, such non-specific binding can produce additional side effects such as weight gain and sedation [1055792].

Several significant limitations exist with currently available medication-based treatments for schizophrenia. First, overall tolerability and efficacy are limited. For example, in the large National Institute of Mental Health (NIMH)-sponsored evaluation of multiple antipsychotics in schizophrenia (CATIE) clinical trial, the time to discontinuation of any medication was within 18 months in 74% of patients, driven by poor efficacy and side effects [1049149]. Second, at least 30% of patients fail to respond to multiple currently available antipsychotic medications; these patients are regarded as having treatment-resistant schizophrenia [300911]. Approximately 50% of these patients are estimated to respond to clozapine, which is the only medication indicated for treatment-resistant schizophrenia [1055796]. The reason for the efficacy of clozapine in these patients is unknown; this atypical antipsychotic exhibits rapid dissociation from the dopamine receptor as well as binding to other receptor types. None of these features is unique, although no other agents have been demonstrated to have similar efficacy [300911]. This unique efficacy for clozapine might relate to activity in the GABA system [1055797]. Not all patients respond to clozapine, and many patients experience associated side effects, including the development of neutropenia, myocarditis and seizures [1055798]. Third, antipsychotics are most effective at targeting the positive symptoms of the disorder. Limited evidence supports the effectiveness of any antipsychotics in the treatment of the negative and cognitive symptoms of schizophrenia [1055799], [1055800], possibly because these symptoms are more related to structural brain changes [1055804]; such symptoms play a major role in influencing functional capacity and quality of life [1055805], [1055806].

Although the therapeutic target for all available antipsychotics has been monoamine neurotransmitters, such as dopamine and serotonin, increasing evidence from postmortem and clinical research in patients with schizophrenia suggests a role of dysfunction in other neurotransmitters, including GABA [1055808], [1055809]. Of the two main GABA receptor types, GABA_A receptors are part of a ligand-gated ion channel complex and GABA_B receptors areGPCRs. These receptors comprise a variety of subunits that determine aspects of their functional role [1056649]. Patients with schizophrenia exhibit a reduction in GABA neuron density and abnormalities in GABA receptors and GABA reuptake sites [1055772], [1055773]. More specifically, there is a reduction (30 to 48%, dependent on cell layer) in mRNA for the synthetic glutamic acid decarboxylase (GAD) enzyme GAD67, a subtype of GAD that is responsible for the production of GABA in parvalbumin-containing interneurons in the prefrontal cortex [1055811]. There is also a substantial increase (> 100%) in GABA_A receptors containing α2 subunits on the initial segments of the axons of pyramidal cells in the dorsolateral prefrontal cortex (the synaptic target of parvalbumin-containing interneurons) [1055814]. These findings have led to the suggestion that drugs targeting α2 subunit-containing GABA_A receptors could be a promising target for the treatment of schizophrenia [1055813]. In addition, studies have demonstrated a marked increase in immunoreactivity for the α2 subunit of the GABA_A receptor on the initial segment of prefrontal pyramidal cells (the site of synapses arising from parvalbumin-containing interneurons) in patients with schizophrenia [1055808]. Deficits of cortical inhibition related to GABA have also been suggested from results of neurophysiological clinical trials, including those using transcranial magnetic stimulation [407898].

Studies describing a role for GABA dysfunction in schizophrenia have been accompanied by studies suggesting beneficial effects of GABAergic drugs in the treatment of the disorder. For example, GABA agonists or compounds that positively and allosterically modulate the GABA receptor, such as benzodiazepines (eg, diazepam or lorazepam), can reduce motor side effects and tardive dyskinesia induced by typical antipsychotics, and have demonstrated some beneficial effects in the prevention of psychotic relapse in patients with schizophrenia [1049165], [1049167], [1049172]. The medicinal use of exogenous GABA, however, is limited by the inability of the neurotransmitter to cross the blood-brain barrier (BBB) [1055815]. GABA modulators, such as benzodiazepines, modulate GABA_A receptors broadly, including those containing the α1 subunit; this modulation produces unwanted effects, such as sedation and tolerance [451562]. Other compounds, such as imidazenil [1049173], that modulate GABA_A receptors containing the α1 but not the α2 subunit, may have beneficial properties without the side effect burden associated with benzodiazepines; however, imidazenil was not developed clinically [1049149]. Another approach has involved the development of a positive allosteric modulator of the α1 subunit-containing GABA_A receptor [1049174], [1055884]. In a pilot, controlled clinical trial evaluating the potential of the α1- (and α1-) specific modulator MK-0777 [1049174], [1055884], the compound produced a greater improvement in performance on several prefrontally mediated cognitive tasks than placebo [1049174]. However, because of observed preclinical toxicity, clinical trials with MK-0777 were terminated [1046010].
BL-1020, which is being developed by BioLineRx Ltd under license from Ramot at Tel Aviv University Ltd and Bar-Ilan Research & Development Co Ltd (Bar-Ilan R&D), is an ester of the typical antipsychotic perphenazine and GABA [980257]. The provision of GABA as an ester in this form was believed to allow transport across the BBB; conjugation of GABA with a fatty amino acid or peptide facilitates this process. Within the CNS, hydrolysis is expected to release GABA and perphenazine, producing the activation of GABA in conjunction with traditional antipsychotic activity [980257]. BL-1020 is a dopamine receptor antagonist [906315], [980257] and a GABA, agonist [980257]. In phase II clinical trials assessing BL-1020 in patients with schizophrenia, clinically meaningful improvements were demonstrated [969895], [1041824], [1044706]. At the time of publication, a phase Ib clinical trial of BL-1020 in patients with schizophrenia was ongoing [1041824].

Synthesis and SAR

BL-1020, a perphenazine GABA conjugate, was synthesized by the coupling of perphenazine and N-tert-butoxycarbonyl-GABA (N-Boc-GABA) [906315]. A mixture of N-Boc-GABA and carbonyldimidazole in DMF was stirred under nitrogen for 1 h. Perphenazine was added, and the mixture was stirred under nitrogen at 90°C for 24 h to produce the BL-1020-Boc derivative in 63% yield. The Boc group was removed under acidic conditions. Adding HCl in ethyl acetate yielded BL-1020 trihydrochloride, which was hygroscopic. Other salts, such as maleate, were less hygroscopic, but the trimesylate salt obtained by direct treatment of the Boc-derivative with methansulfonic acid was as effective as a novel, orally active antipsychotic drug. The trimesylate salt was selected for use in clinical trials [906315]. Similar syntheses of BL-1020 and its salts were published in WO-2003026563, WO-2005092392 and WO-2006131923.

Preclinical development

As dopamine blockade can result in elevated prolactin levels, the effect of treatment with antipsychotics on prolactin secretion was studied in male Wistar rats [906315], [980257]. Prolactin levels were elevated by a higher dose of perphenazine (5 mg/kg ip), fluphenazine (7.5 mg/kg ip) and BL-1020 (7 mg/kg in equimolar to the perphenazine dose) at 1 and 2 h post-dose (p < 0.05 for all agents versus vehicle control) [906315]. Prolactin elevation, at 1.5 and 3 h post-dose, was also observed when equimolar doses of BL-1020 (7, 14 and 28 mg/kg) and perphenazine (5, 10 and 20 mg/kg) were administered orally by gavage (p < 0.05 for all doses versus vehicle control) [906315]. In a set of similar experiments, equivalent results were achieved 2 and 3 h after treatment with equimolar doses of perphenazine (4.5 and 9.0 mg/kg po) and BL-1020 (po) (p < 0.01 at both time points and for both agents versus vehicle control) [980257]. These results indicated that BL-1020 has activity as a dopamine receptor antagonist [906315].

The effect of BL-1020 treatment was assessed in a rat psychosis model of d-amphetamine-induced hyperactivity [906315], [980257], [982969], [982970], [982971]. Treatment with GABA (1 mg/kg po) had no effect on animal hyperactivity, while perphenazine treatment (2.5 mg/kg po) reduced hyperactivity, but induced sedation and cataleptic behavior [906315]. BL-1020 (equimolar to the perphenazine dose po) reduced hyperactive behavior with minimal sedation and no catalepsy [906315]. A second set of amphetamine-induced hyperactivity experiments were conducted that used a higher dose of perphenazine (3.2 mg/kg po) and BL-1020 equivalents [980257]. Most acute effects of BL-1020 were comparable with those of perphenazine, although BL-1020 reduced head movements to normal levels and perphenazine reduced movements to subnormal levels (p < 0.01 for both agents versus vehicle controls). A subchronic amphetamine-induced hyperactivity model was also used. After 17 days, treatment with BL-1020 (3.3, 6.6 and 13.3 mg/kg po, qd) reduced hyperlocomotion by 24, 58 and 54%, respectively; this effect was significant at the two highest doses (p < 0.01 versus vehicle control). At equimolar concentrations, hyperlocomotion was also reduced significantly by perphenazine treatment at all dose levels [980257].

In male Sprague-Dawley rats, the effect of BL-1020 (0.3, 1, 3 and 10 mg/kg sc) on dopamine and ACh release in the prefrontal cortex and hippocampus was evaluated [980257]. BL-1020 increased dopamine efflux in both regions in a dose-dependent manner; this effect was significant for all doses (p < 0.005 versus vehicle control) except the 0.3-mg dose. The compound did not affect ACh levels [980257]. BL-1020 bound strongly to D₃ receptors, particularly the D₃L, D₃S and D₃ receptors (Kᵢ = 0.066, 0.062 and 0.048 nM, respectively) [980257]. The interaction between BL-1020 and the D₃ and 5-HT₂A receptors (Kᵢ = 0.066 and 0.211 nM, respectively) was greater than that observed with perphenazine (Kᵢ = 0.182 and 1.04 nM, respectively). BL-1020 also bound strongly to the histamine H₁ receptor (Kᵢ = 0.473 nM) and demonstrated agonist activity at the GABAₐ receptor (Kᵢ = 3.74 μM), but had no activity at the GABAₐ receptor [980257].

The most recently conducted preclinical study of BL-1020 involved the administration of the agent (po, qd for 15 days) to rats pre-exposed to the NMDA receptor antagonist phencyclidine (2 mg/kg ip, bid for 7 days followed by a 7-day drug-free period) to induce deficits in object recognition memory [1032253]. BL-1020 significantly attenuated the behavioral effects caused by phencyclidine, increasing novel object exploration time compared with familiar object exploration time on days 8 and 15 (p < 0.05 and 0.01 versus vehicle control, respectively), indicating that BL-1020 may have beneficial effects on cognitive function [1032253].

Toxicity

No toxicity was associated with BL-1020 treatment in the studies in rats described in the Preclinical development section [906315], [982969], [982970]. Behavioral and physiological responses to single, increasing doses of
BL-1020 (3, 6, 10, 13, 20 and 30 mg/kg po) were assessed using the Irwin test in male Wistar rats [980257]. No toxicity was observed at doses up to 20 mg/kg; at doses of 30 mg/kg, sedation and abnormal rolling gait were induced. Decreased reactivity to touch was also detected at the 30-mg/kg dose [980257].

Motor side effects including extrapyramidal symptoms were analyzed by studying the appearance of cataleptic behavior in male Wistar rats following the administration of antipsychotic drugs [906315], [980257]. Cataleptic behavior was assessed between 30 and 420 min following the single-dose administration of perphenazine (5 mg/kg ip), fluphenazine (7.5 mg/kg ip) or BL-1020 (7 mg/kg [equimolar to the perphenazine dose] ip) [906315]. Cataleptic behavior was observed in the perphenazine- and fluphenazine-treated rats, but not in those treated with BL-1020. In addition, little or no sedation was evident in the animals administered BL-1020 compared with the perphenazine- and fluphenazine-treated rats, which were ataxic and immobile. Perphenazine (5, 10 and 20 mg/kg po) resulted in significantly higher cataleptic behavior than equimolar oral doses of BL-1020 (p < 0.05 for perphenazine versus BL-1020), with concurrent increased sedation occurring in perphenazine-treated rats [906315]. In a separate comparative study, the acute administration of perphenazine (3.3 mg/kg po) caused cataleptic behavior and had a sedative effect at 4 h post-dose and 150 min after the administration of amphetamine; an equimolar dose of BL-1020 did not induce cataleptic behavior (p < 0.05 versus perphenazine) [980257].

In a subchronic dosing study, rats received perphenazine (1.6, 3.2 and 6.4 mg/kg po, qd) or equimolar doses of BL-1020 (3.3, 6.6 and 13.3 mg/kg po) for 17 days, followed by a single dose of amphetamine (3.0 mg/kg ip) administered 2 h after the last dose of antipsychotic drug. On day 1, BL-1020 at doses of 6.6 or 13.3 mg/kg was associated with a significantly reduced manifestation of cataleptic behavior compared with equimolar perphenazine (p < 0.001), which increased catalepsy in a dose-related manner. Reduced catalepsy induced by BL-1020 was maintained after prolonged administration (15 days) of the 3.3- and 6.6-mg/kg doses, and catalepsy was observed only at the highest administered dose of BL-1020 (13.3 mg/kg) [980257].

In rats, BL-1020 traversed the BBB [906315], [980257], [982971]. The presence of intact BL-1020 and GABA in the brain was assessed after the single-dose administration of [14C]BL-1020 (5 mg/kg po) to rats [980257]. At 15 min post-dose, a significant level of GABA and a smaller level of intact BL-1020 could be detected in the brain by HPLC-radiochromatography. After 30 min, the ratio of BL-1020 to GABA had decreased and, at 1 h, no BL-1020 could be detected. The quantity of GABA increased from 15 to 30 min and remained at a similar level after 4 h. There was also some evidence of the presence of GABA metabolites [980257].

A phase I, two-part clinical trial (ClinicalTrials.gov identifier: NCT00480246; BL-1020.02) assessed the pharmacokinetics of BL-1020 in conjunction with receptor occupancy in healthy male volunteers (n = 20) [1048059]. In the first part of the trial, the volunteers received single-dose BL-1020 (16 to 32 mg po) [984717], [1048059] and, in the second part, the volunteers received single-dose perphenazine (8 mg po) followed by treatment with single-dose BL-1020 (16 or 32 mg po) after a 7-day washout period [1048059]. BL-1020 could not be quantified in plasma from 2 h post-dose onward; therefore, the pharmacokinetic analysis was restricted to plasma concentrations of perphenazine. Results from the first part of the trial indicated that the average plasma levels of perphenazine after single-dose BL-1020 were dose dependent. In the second part of the trial, equimolar doses of BL-1020 and perphenazine had different early pharmacokinetics. However, plasma perphenazine concentrations with equimolar BL-1020 and perphenazine achieved a similar plasma concentration from 4 h post-dose onward. Pooled data from all BL-1020 cohorts revealed that exposure to perphenazine was approximately dose proportional (Cmax = 0.184, 0.310 and 0.378 ng/ml and AUC0-∞ = 3.08, 4.00 and 6.47 ng-h/ml for doses of 16, 24 and 32 mg, respectively). Perphenazine released from the metabolism of BL-1020 had a slower plasma elimination time (t1/2 = 12.3 to 15.9 h) than directly administered perphenazine (t1/2 = 8.72 h); however, the Tmax value was approximately equivalent (Tmax = 2.00, 1.00, 3.00 and 1.00 h for BL-1020 doses 16, 24 and 32 mg and a perphenazine dose of 8 mg, respectively) [1048059].

**Clinical development**

**Phase I**

A phase I, randomized, double-blind, placebo-controlled, parallel-assignment, single-center, dose-escalating clinical trial assessed single-dose BL-1020 (4, 8, 16, 24, 32 and 40 mg po) in healthy male volunteers (n = 48). A dose-dependent elevation of prolactin levels was observed [765897], [982968].

A phase I, non-randomized, open-label, active-controlled, parallel-assignment, single-center, two-part clinical trial (NCT00480246; BL-1020.02) assessed BL-1020 in healthy male volunteers (n = 20) [1048059]. In the first part of the trial, the volunteers (n = 12) received single-dose BL-1020 (16, 24 or 32 mg po) [984717], [1048059] and, in the second part, the participants (n = 8) received...
perphenazine (8 mg po) followed by treatment with single-dose BL-1020 (16 or 32 mg po) after a 7-day washout period [1048059]. The trial provided information on the brain activity of BL-1020 [984717], [1048059]. Through the measurement of changes in the uptake of the D_1 receptor antagonist [^{11}C]raclopride, striatal levels of BL-1020 binding to D_2 receptors were evaluated [1048059]. In both parts of the trial, a dose-dependent reduction of [^{11}C]raclopride uptake was observed at 6 and 24 h post-dose. A comparison of equimolar doses of BL-1020 and perphenazine at 6 h post-dose revealed that treatment with 8 mg of perphenazine resulted in a higher D_1 receptor occupancy than 16 mg of BL-1020; however, this difference was not significant, and there was no difference in occupancy observed at 24 h post-dose. Pooled data from both parts of the trial revealed that the highest dose of BL-1020 (32 mg) produced a D_2 receptor occupancy of 34% at 24 h post-dose; this result was significant compared with the 16-mg dose of BL-1020 (~ 20% occupancy; p < 0.05) and the 8-mg dose of perphenazine (~ 20% occupancy; p < 0.01). A linear relationship was observed between D_2 receptor occupancy and BL-1020 dose per kg of body mass. Moreover, at 4 h post-dose, plasma prolactin levels were dose dependent. The equimolar dose of perphenazine had a faster effect on the prolactin levels than BL-1020, but this difference could no longer be observed at 7 h post-dose. With chronic once-daily dosing, a 32-mg dose of BL-1020 was estimated to result in 52 to 66% D_2 receptor occupancy [1048059].

**Phase II**

A phase IIa, non-randomized, open-label, uncontrolled, single-group-assignment, multicenter, 6-week clinical trial (NCT00480571; BL-1020 II) assessed BL-1020 in hospitalized patients (n = 36) with chronic schizophrenia or schizo-affective disorder [969895], [1048056]. Doses of BL-1020 (po, qd) were increased from 20 mg on day 1 to 30 mg on day 4 to 40 mg on day 7, based on tolerability; 97% of patients were titrated to 30 mg and 86% to 40 mg [969895]. Patients treated with BL-1020 demonstrated significant (p < 0.001) and clinically relevant improvements according to the PANSS score, with a decrease from baseline of 21.8 (mean baseline score = 85.6), as well as improvement on the positive, negative and general psychopathology subscales. A clinically meaningful improvement in PANSS score (≥ 20% reduction in total PANSS score) was observed in 61.1% of patients. Significant improvement was also demonstrated as measured by the Clinical Global Impression of Severity (CGI-S) and Change (CGI-C) scales, with a mean decrease from baseline of 1.2 on the CGI-S scale (p < 0.001) and 86.1% of patients rated as improved (score of 1, 2 or 3) on the CGI-C scale. At day 42, > 70% of patients were considered to be suitable for discharge from the trial [969895]. According to the NIH clinical trials registry, a higher-dose cohort (patients titrated from 30 to 50 mg po,qd) was also included in the protocol for this trial; inclusion of this cohort would increase the total enrollment to an estimated 90 patients with chronic schizophrenia or schizo-affective disorder. Data from this part of the trial were not available at the time of publication.

A phase IIb, randomized, double-blind, placebo- and active-controlled, parallel-assignment, multicenter, 6-week clinical trial (NCT00567710; BL-1020 IIb; EAGLE) assessed BL-1020 (10 or 20 to 30 mg po, qd) and risperidone (2 to 8 mg po, qd) in patients (n = 363) with schizophrenia who were experiencing an acute exacerbation of psychosis [1041824], [1044706]. A significant reduction in PANSS score was achieved in the BL-1020 high-dose (20 to 30 mg) cohort compared with placebo (decrease of 23.6 versus 14.4; p = 0.002); efficacy was also demonstrated when analyzing the CGI-S and CGI-C parameters [1041824]. Cognitive function was also assessed in the trial using the Brief Assessment of Cognition in Schizophrenia (BACS) test, which assesses verbal memory, digit sequencing, token motor task, verbal fluency, symbol coding and the ability to complete a 'Tower of London' puzzle [1044706]. Patients receiving high-dose BL-1020 demonstrated clinically relevant and significant improvements in the BACS score (9.27 points) compared with placebo (6.01 points; p = 0.027 versus high-dose BL-1020) and risperidone (6.2 points; p = 0.027 versus high-dose BL-1020) [1044706].

At the time of publication, a phase IIb, randomized, double-blind, active-controlled, parallel-assignment, multicenter, 6-week clinical trial (NCT00722176; BL-1020 IIb extension) was listed on the NIH clinical trials registry as an extension of the EAGLE trial. In this trial, hospitalized patients (expected n = 220) with schizophrenia who had been treated previously in the active groups of the EAGLE trial were assigned to BL-1020 (10 or 10 to 30 mg po, qd) or risperidone (target dose of 8 mg po, qd). The primary outcome measures were changes from baseline in vital signs, laboratory and ECG evaluations, physical or neurological examination, Extrapyramidal Symptom Rating Scale (ESRS; assesses Parkinsonism, akathisia, dystonia and tardive dyskinesia) score, and the incidence of adverse events and withdrawals. BioLineRx expected this trial to be completed in October 2009; however, no safety or efficacy data were available at the time of publication.

**Side effects and contraindications**

In the phase I, dose-escalation clinical trial in healthy male volunteers (n = 48), BL-1020 was well tolerated at all doses [982968]. Treatment with BL-1020 did not induce psychological symptoms such as anxiety, depression, Parkinsonism or akathisia, or any laboratory or ECG abnormalities. Facial twitching and sleepiness were experienced by one volunteer receiving 40 mg of BL-1020 at 24 h post-dose. Therefore, 40 mg was regarded as the MTD [982968].

In the phase I, two-part clinical trial in healthy volunteers (n = 20), there were no significant changes in ECG, vital signs, or laboratory or physical examination parameters [984717], [1048059]. In the first part of the trial, a total of 23 treatment-emergent adverse events were reported by 11 volunteers. In the second part of the trial, 31 treatment-emergent adverse events were reported by 8 volunteers [1048059]. The most frequent adverse events in the volunteers receiving BL-1020 were fatigue (10 events),
polyuria (4 events), nasopharyngitis (3 events), epistaxis, muscle spasms and dizziness (all 2 events). All of the adverse events were mild or moderate in intensity [1048059].

In the phase IIa clinical trial in hospitalized patients (n = 36) with chronic schizophrenia or schizo-affective disorder, there were no clinically relevant effects on vital signs, ECG or laboratory parameters [969895], or changes in weight [1048056]. Mean total scores on the ESRS were unchanged [969895]. Notably, only four patients withdrew from the trial, one each because of lack of efficacy, withdrawal of consent, failure to return for visit and occurrence of an adverse event. Adverse events that occurred in > 5% of patients were insomnia (6 patients) and extrapyramidal disorder, headache, Parkinsonism, tremor, and hyperprolactinemia (each in 3 patients). Other adverse events included dizziness, akathisia, dystonia and decreased WBC count, each of which occurred in one patient [969895].

In the phase IIb clinical trial in patients (n = 363) with schizophrenia, no serious adverse events were observed in the high-dose (20 to 30 mg) BL-1020 cohort, whereas events occurred in 3.3 and 6.5% in the risperidone and placebo cohorts, respectively [1041824]. Withdrawals caused by adverse events were similar in the placebo and high-dose BL-1020 cohorts (4.3%) and higher in the risperidone cohort (8.8%). No significant or clinically relevant changes in body weight, glucose levels or lipids, or measurements of ECG, laboratory or vital signs were observed. The incidence of cardiovascular, sexual, psychiatric, autonomic and gastrointestinal adverse events was low in the BL-1020 cohorts and was not increased compared with placebo. A slight increase in the ESRS scale was observed in the high-dose BL-1020 cohort, which did not differ significantly from the risperidone cohort [1041824].

**Patent summary**

BL-1020 was first claimed jointly by Ramot at Tel Aviv University Ltd [Tel Aviv University] and Bar-Ilan R&D in WO-03026563. US granted equivalents include US-07544681, which specifically claims BL-1020 (claim 2, page 47) and is due to expire in December 2023 following a US154 extension; and continuation-in-part US-07598239, which expires in September 2022. At the time of publication, the European equivalent application (EP-01429844) was pending grant. WO-03026563 and all members of its patent family were presumably part of BioLineRx's 2004 worldwide licensing agreement for the development of the drug [547477].

BioLineRx, Bar-Ilan R&D and Tel Aviv University are subsequently named on WO-2006131923, disclosing novel salts of BL-1020.

**Current opinion**

The development of BL-1020 has been based on a background of more than a decade of substantial neuroscience research demonstrating the significant involvement of abnormalities in GABAergic function in schizophrenia, as well as several clinical observations indicating that augmenting GABA function is likely to result in improved tolerability of dopamine antagonist medication. Several approaches have been undertaken to target GABAergic function in schizophrenia, including efforts to specifically target the GABA \( \alpha_{2} \) (and \( \alpha_{7} \)) components, as with the compound MK-0777. However, targeting GABA function is a relatively novel area of R&D as most therapeutics in schizophrenia target other neurotransmitter systems, such as glutamate.

The promise of targeting GABA function is evident from the preclinical data for BL-1020. The compound demonstrated a favorable preclinical profile, with evidence of activity that was likely to be antipsychotic, but unlikely to have several of the substantial side effects observed with equivalent antipsychotic medications, such as perphenazine. The preclinical behavior of BL-1020 is consistent with its receptor binding profile.

In early clinical trials conducted with BL-1020, the preclinical results of the compound appear to have been similarly demonstrated. In humans, the dopamine receptor occupancy results were consistent with the preclinical profile, and provided confirmation that the drug is active in the CNS and has dopaminergic activity, but that the profile of CNS effects differs from that of perphenazine [906315]. At the time of publication, the pharmacokinetic information available for BL-1020 also suggested that the compound was likely to be a clinically practical entity given its once-daily dosing; such a dosing regimen is a highly desirable aspect of treatment in schizophrenia, for which treatment is likely to be long-term and often in patients with poor compliance.

The main limitation of the research with BL-1020 is the lack of substantial clinical outcome data. Future phase II and III clinical trial data will be critical in determining whether the compound has suitable efficacy in humans. It is unlikely that the drug will fail to exhibit antipsychotic efficacy; at minimum, the administration of BL-1020 will provide patients with a dose of perphenazine, a well-established and active antipsychotic drug. The critical questions of future clinical trials relate to whether the GABA component of BL-1020 will enhance effectiveness.

BL-1020 may prove to be therapeutically advantageous compared with previously available treatments in two areas. First, the combination of GABA with perphenazine may substantially ameliorate the extrapyramidal side effects, including tardive dyskinesia, that can occur with typical antipsychotics such as perphenazine. If BL-1020 were to have this effect, the compound would be therapeutically useful because perphenazine is effective and does not have substantial metabolic and weight-related side effects that occur with some of the second-generation atypical antipsychotic medications. The GABA component of the drug would be directly contributing to...
the successful amelioration of major side effects associated with perphenazine. A second, and more ambitious, outcome for BL-1020 may be that the GABA component contributes to enhancing efficacy in the overall treatment of schizophrenia, including improvement in positive, negative and cognitive symptoms. Although speculative, a deficit of GABAergic neuronal activity has been suggested by various basic research findings, and drugs that act only at dopamine receptors have limited capacity to ameliorate these deficits. The exception is clozapine, which is effective in treatment-resistant schizophrenia, with an action that potentially occurs through the GABA system [1055797]. The administration of GABA directly into the CNS through BL-1020 offers the possibility that a direct effect on the GABA system may improve symptoms of schizophrenia to a greater degree than that of any currently available antipsychotic medication or to an equivalent degree to that observed with clozapine. If the improvement in symptoms were similar to that with clozapine, BL-1020 would advantageous given that clozapine is highly effective, but has substantial treatment-limiting side effects [1055798].

Thus, BL-1020 rapidly could become a highly prescribed and valuable treatment option, although considerable challenges must be overcome with the drug. One of these challenges relates to whether the effects of BL-1020 on the GABA system will be sufficiently specific to have therapeutic value. BL-1020 treatment should result in a generalized increase of GABA within the CNS, with nonspecific increased activity at all GABA receptor subtypes. Studies performed in schizophrenia suggest that the deficit of GABA is not generalized and occurs at a subtype of GABAergic neurons [1056782]. It is possible that a global increase in GABA will have specific activity at receptors that are suboptimally active without marked effects at other receptors, but it is also possible that effects on other receptors may lead to substantial side effects. These issues will only be resolved with further clinical trials.

Deals

BioLineRx Ltd

In May 2004, BioLineRx acquired compounds for the treatment of neurological disorders and cancer from Tel Aviv University and Bar-Ilan R&D [547477].

Israeli Government

In December 2004, BioLineRx received funding from the Israeli Government for the development of preclinical candidates as part of an initiative for the advancement of the Israeli Biotech industry. The grant was worth US $21 million, which brought the total of funds available for BioLineRx’s development to US $35 million [647957].

Development status

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<th>Developer</th>
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Associated patent

Title: Conjugated anti-psychotic drugs and uses thereof.
Assignees: Ramot at Tel Aviv University Ltd (Tel Aviv University); Bar-Ilan University
Publication: WO-03026563 03-APR-03
Inventors: Nudelman A, Raphaeli A, Gil-Ad I, Weizman A.

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but did not affect ACh levels. The agent bound strongly to D₃ in the prefrontal cortex and hippocampus in a dose-dependent manner, chronically at a dose of 13.3 mg/kg. BL-1020 increased dopamine efflux.

•• Describes a phase I, non-randomized, open-label, active-controlled parallel-assignment, single-center, two-part clinical trial (NCT00480246) that assessed BL-1020 in healthy male volunteers. The highest dose of BL-1020 (32 mg) produced a D₃ receptor occupancy of 34% at 24 h post-dose, and a linear relationship was observed between D₃ receptor occupancy and BL-1020 dose per kg of body weight. There were no significant changes in ECG, vital signs, or laboratory or physical examination parameters.

2007 doi:10.1016/j.euroneuro.2007.07.009

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