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Effectiveness and safety of blonanserin for improving social and cognitive functions in patients with first-episode schizophrenia: a study protocol for a prospective, multicentre, single-arm clinical trial

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ABSTRACT

Introduction Both the pharmacological characteristics of blonanserin and its related small sample size studies suggest that blonanserin could alleviate social and cognitive dysfunctions in patients with schizophrenia. However, no large sample size studies have been performed so far. This study aimed to investigate the effectiveness and safety of blonanserin in improving social and cognitive functions in patients with first-episode schizophrenia.

Methods and analysis This is a prospective, multicentre, single-arm clinical trial. A total of 188 patients with first-episode schizophrenia will be enrolled and will undergo a 0–7 day washout period before blonanserin administration. Doses of blonanserin will first be set to 4 mg P.O. twice per day after meals and gradually increased to 8–16 mg/d P.O., depending on patient's age and symptoms, for 26 weeks. Maximum dose of blonanserin will not be exceeding 24 mg/day. The primary endpoint of the study is the changes of Personal and Social Performance (PSP) score in patients from baseline to week 26. Secondary endpoints include changes in MATRICS consensus cognitive battery (MCCB), Paced Auditory Serial Addition Test (PASAT), grooved pegboard test (GPT), Positive and Negative Syndrome Scale (PANSS) total score and PANSS 5-factor subscale scores. Other endpoints include changes of serum brain-derived neurotrophic factor (BDNF) at corresponding visits and MRI results. Moreover, incidence of adverse events, changes in endocrine and metabolic profiles, renal, hepatic and sexual functions and extrapyramidal symptoms will be strictly monitored and recorded.

Ethics and dissemination The study was approved by the ethics committee of the leading site Peking University Sixth Hospital (No. 2018–18), and all included patients are requested to provide written informed consent before enrolment. The study will be conducted according to the principles of the Declaration of Helsinki and follow the principles for clinical research.

Trial registration number NCT03784222.

Strengths and limitations of this study

► This is the first multicentre, large-scale clinical trial focusing on the effectiveness of blonanserin on improving social and cognitive functions in Chinese patients with first-episode schizophrenia.
► Both objective measurements (serum brain-derived neurotrophic factor and multimodal MRI) and behavioural indicators (Personal and Social Performance, MATRICS consensus cognitive battery and Positive and Negative Syndrome Scale) will be analysed.
► The trial is a single-arm study since placebo is not recommended for patients with first-episode schizophrenia given ethical considerations.

INTRODUCTION

Schizophrenia is a serious mental disorder with unknown causes. According to several analyses based on the symptoms in recent years, the clinical manifestations of schizophrenia are divided into five dimensions, including positive symptoms, negative symptoms, cognitive symptoms, hostility and anxiety/depression. Schizophrenia is believed to be related to cognitive impairments.[1] Critical achievements in schizophrenia studies have highlighted the significance of cognitive deficiencies. Patients with schizophrenia usually show a series of advanced cognitive deficiencies, including attention, executive function, working memory and episodic memory.[2] Cognitive impairment in schizophrenia patients is believed to be independent of positive and negative symptoms.[1] Long-term studies of schizophrenia have shown that large number of patients still have cognitive impairment after the improvement

or disappearance of psychotic symptoms, which are significantly associated with social functional disability.[1] Therefore, improving social and cognitive functions is one of the primary goals of therapeutic interventions.[2]

Blonanserin, a novel compound synthesised by Sumitomo Pharmaceuticals (Suzhou) Co., has unique pharmacological characteristics. It has high affinity for dopamine D_2 receptors, 5-HT$_{2A}$ receptors and dopamine D_3 receptors, with average inhibitory constants of 0.14, 0.49 and 0.81, respectively.[3] It is currently believed that dopamine D_3 receptors are expressed in mesolimbic and cortical areas that are related to cognition in schizophrenia.[4] A large number of preclinical studies have suggested that dopamine D_3 receptors affect cognitive function mainly by mediating prefrontal cortex function in the treatment of cognitive impairment in schizophrenia.[5–7] 5-HT$_{2A}$ receptor is also a critical contributor in a number of cognitive processes.[8] A preclinical study suggested that augmentation of dopaminergic neurotransmission via inhibition of both D_3 and 5-HT$_{2A}$ receptors in the medial prefrontal cortex may play a significant role in the ameliorating effect of blonanserin on cognitive impairment in experimental schizophrenia.[9]

Consistent with preclinical data, Hori *et al*[10] found that 8 weeks of blonanserin treatment resulted in improved cognitive function as well as daily living and work skills in 39 Japanese acute schizophrenia cases, while the control drug risperidone only improved work skills. In another clinical study of 26 Japanese patients with schizophrenia, 8 weeks of blonanserin treatment at 8–24 mg/day resulted in improved cognitive function.[11] Taken together, both the pharmacological characteristics of blonanserin and small sample size studies suggested that this drug could improve social and cognitive functions in patients with schizophrenia.

It is generally admitted that schizophrenia patients with shorter duration of untreated psychosis have better prognoses.[12 13] Drug intervention in patients with schizophrenia immediately after the first episode is of great significance in improving cognitive function and prognosis. A phase III clinical study in Chinese patients demonstrated its effectiveness and safety of blonanserin in treating schizophrenia. In February 2017, blonanserin was commercially approved in China. Based on the pharmacological characteristics and previous studies of blonanserin, we performed a clinical trial with a large sample size to further validate the effectiveness of blonanserin for improving both social and cognitive functions as well as the prognosis and life quality of patients with schizophrenia.

This study aimed to investigate the improvement of social and cognitive functions in patients with first-episode schizophrenia after blonanserin treatment. Personal and social performance (PSP) and MATRICS consensus cognitive battery (MCCB) scales were introduced to assess behavioural changes in patients with first-episode schizophrenia under blonanserin treatment. Multimodal MRI will be used to reveal brain structural and functional changes in blonanserin-treated patients. Benefits of blonanserin treatment for first-episode schizophrenia patients will be further determined if both behavioural and objective imaging indicators are improved.

METHODS AND ANALYSIS
Study design
This is a prospective, multicentre, single-arm clinical trial. This study was approved by the ethics committee of the leading site, Peking University Sixth Hospital, and registered on ClinicalTrials.gov. All participants are requested to provide written informed consent before enrolment. The study will be conducted according to the principles of the Declaration of Helsinki and follow all existing principles for clinical research.

Study population
Patients will be recruited from nine hospitals in China. Inclusion criteria are as follows: (1) schizophrenia diagnosed according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) or International Classification of disease-10 (ICD-10); (2) Positive and Negative Syndrome Scale (PANSS) score ≥70; (3) age of 18–45 years; (4) disease course less than 5 years; (5) nine or more years of education; (6) no prior systematic antipsychotic treatment, single continuous treatment less than 6 weeks, or total treatment duration less than 6 months; (7) capable of reading and understanding Chinese characters; (8) provide written informed consent. Exclusion criteria are as follows: (1) severe or unstable health conditions judged by investigators, including but not limited to cardiovascular, cerebrovascular, liver and kidney diseases; (2) loss of consciousness for over 1 hour due to any cause in the past year; (3) current drug abuse (in the past 3 months) or substance dependence; (4) planning for pregnancy, actual pregnancy or lactation in women; (5) history of suicide attempt, severe suicidal ideation or behaviour; (6) contraindications for blonanserin; (7) prior treatment with blonanserin; (8) mental retardation; (9) participation in other trials within 30 days before enrolment; (10) medical conditions that might affect evaluation of drug effectiveness; (11) required hospitalisation or intensive care due to deterioration of physical conditions; (12) severe muscle rigidity or Parkinson's disease; (13) abnormal results of laboratory tests (routine blood test, urine analysis and haematology and biochemistry tests) with clinical significance; (14) abnormal ECG results with clinical significance determined by the investigators; (15) continuous usage of anticholinergic drugs or sedatives in the past 3 months; (16) electroconvulsive therapy (ECT) in the past 3 months; (17) long-acting antipsychotic treatment in the past 3 months; (18) difficulties in drug swallowing; (19) other medical conditions that are determined to be unsuitable for enrolment. Sample size was calculated based on average changes in PSP score before and after blonanserin treatment. Based on previous studies, differences in PSP score is expected

to be 6.4±17.8 before and after blonanserin treatment. The PSP score without medication was expected to increase by two points. Using one-sided, single sample t-test, with an α of 0.025 and a statistical power of 80%, the sample size was estimated at 131. Taken 30% drop-out rate into consideration, the sample size of the treatment group was set to 188. Sixty patients in the intervention group will be scheduled for multimodal MRI and serum brain-derived neurotrophic factor (BDNF) examinations. Since the results of these two examinations may fluctuate due to potential background noises,[14] the control group will include 60 patients (1:1 to the treatment group) to compare with the treatment group in order to eliminate background noise.[14] Taken together, the total sample size of the study was set to 248.

Intervention

Since placebo is not recommended for patients with first-episode schizophrenia due to ethical considerations,[15] a single-arm design is used in this trial. Blonanserin (Sumitomo Pharmaceuticals (Suzhou) Co., Suzhou, China) will be administered in the treatment group. Before receiving blonanserin treatment, the patients will undergo a 0–7 days washout period. Patients with no previous antipsychotic treatment could waive the washout period. Blonanserin will be initiated at 4 mg P.O. twice per day after meals, and the dose will be gradually increased to and maintained at 8–16 mg/d P.O. twice per day after meals. The dose will be adjusted (increased or decreased) properly according to the patient's age and symptoms. The maximum daily dose should not exceed 24 mg and the duration of treatment will be 26 weeks.

During the study period (baseline and during treatment), the following drugs are not allowed: (1) other antipsychotics, except for short-term use of haloperidol injection and olanzapine orally disintegrating tablets in week 2–8 after enrolment; (2) mood stabilisers, antidepressants, 5-HT1A receptor antagonists, cognitive enhancers, antidementia agents and antiepileptic products that affect cognition; (3) other investigational drugs; (4) cytochrome P3A4 blockers (azoles, HIV protease blockers, etc.), excluding those for external use; (5) traditional Chinese herbs for central nervous system diseases; (6) grapefruit drink or food that contains hyperforin. The empirical use of drugs for extrapyramidal symptoms will also be prohibited. Usage of other therapies, including ECT, systemic psychotherapy and physical therapies (eg, transcranial magnetic therapy) will also be prohibited. Drugs that the investigators believe to be essential, including benzodiazepines (lorazepam, oxazepam and alprazolam), anticholinergics and hypnotics, could be used during the study but have to be recorded. The use of benzodiazepines is prohibited 12 hours before neurocognitive tests (including MCCB, paced auditory serial addition test (PASAT) and grooved pegboard test (GPT)).

Baseline and washout period assessment

Demographic data, medical history, medication history and living history (including living habits and social psychological habits), smoking history, family history, suicide history, vital signs, laboratory tests, pregnancy tests, ECG data and PANSS will be collected.[16] In addition, personal and social function levels (using PSP scale score) and neurocognitive function (evaluated by the PASAT, GPT and MCCB scales) will be evaluated.[17–19] Multimodal MRI and serum BDNF detection will be performed. The Abnormal Involuntary Motor Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS) and Arizona Sexual Experience (ASEX) Scale and combined usage of drugs in patients will be recorded.[16]

Primary study endpoint and evaluation

The primary endpoint is social function improvement evaluated by PSP scale at the end of blonanserin treatment.

Secondary study endpoints and evaluation

Secondary endpoints include the following: (1) changes in PSP score after intervention from baseline at corresponding visits (baseline, week 8 and week 26); (2) changes in MCCB score at the end of the intervention; (3) changes in MCCB score at 8 and 26 weeks of blonanserin treatment; (4) changes in the number of correct answers in the PASAT scale at the end of the intervention; (5) changes in completion time of each hand in the GPT from baseline at the end of the intervention; (6) changes in PANSS total score at the end of the intervention; (7) changes in PANSS five-factor subscale scores at the end of the intervention. Other indicators include (for only 60 patients in the treatment group) the following: (1) changes in multimodal MRI result at corresponding visits and at the end of the intervention, and changes of grey matter volume, white matter volume, task-related function area (by fMRI), task-related function connection and resting-state function connection at corresponding visits and the end of the intervention; (2) differences in multimodal MRI results between treatment and normal control groups at baseline; (3) changes in serum BDNF at the end of the intervention; (4) changes in serum BDNF at corresponding visits; (5) differences in serum BDNF between the intervention and normal control groups at baseline. Patients in the normal control group (60 individuals) will undergo MRI examination to eliminate background noises. Criteria for inclusion in the normal control group are: (1) no mental disease; (2) age of 18–45 years; (3) nine or more years of education; (4) no personal history or family history of mental diseases; (5) no severe health problems; (6) cooperation in all examinations; (7) provide written informed consent. Table 1 presents the detailed study procedures and figure 1 shows the diagram of this trial.

Table 1 Study procedures

Item	Screening and washout periods† Day −7 till the day before inclusion	Baseline Day 0	Visit 1 Week 2±3 days	Visit 2 Week 4±3 days	Visit 3 Week 8±3 days	Visit 4 Week 12±7 days	Visit 5 Week 16±7 days	Visit 6 Week 21±14 days	Visit 7 or discontinuity of the trial after 8 weeks of treatment Week 26±14 days
Signing of the informed consent form*	X								
General information of subjects*	X								
Diagnosed as schizophrenia	X								
Medical history*	X								
Urine pregnancy test	X								X
Distribution of the study drug		X	X	X	X	X	X	X	
Recovery of the study drug			X	X	X	X	X	X	X
PSP		X			X	X			X
Neurocognitive test battery†		X			X				X
PANSS‡	X		X	X	X	X			X
Vital signs‡	X				X	X			X
Height‡	X								
Weight‡	X				X	X			X
Laboratory examination‡	X			X	X				X
ECG‡	X			X	X				X
Multimodal MRI*		X§			X¶				X¶
Serum BDNF*		X**			X††				X††
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events*	X	X	X	X	X	X	X	X	X
AIMS/BARS/SAS		X	X	X					X
ASEX		X	X	X					X

*Both the treatment and normal control groups will undergo this examination.
†Patients qualified in the screening will proceed directly to the washout period. Subjects with no prior use of antipsychotics before the screening will not be allowed to use any antipsychotics other than the investigational product from the start of the screening till the end of the treatment period. Patients who have been using antipsychotics before the screening will be required to gradually discontinue such drugs as appropriate and completely discontinue them 1 day before the use of the investigational product. On the start of the treatment period, all subjects will not be allowed to use any antipsychotics other than the study drug. The neurocognitive test battery includes MCCB, PASAT and Grooved Pegboard Test.
‡Results acquired 7 days before the signing of the informed consent form may also be used in the screening period and at baseline as determined by the investigators.
§Only 60 patients in the treatment group will undergo this examination, which is applied to all 60 participants in the normal control group.
¶Only the 60 patients in the treatment group with MRI examination at baseline will undergo this examination.
**Only the 60 patients in the treatment group with MRI examination, and 20 out of the 60 patients in the normal control group will undergo this examination.
†† Only the 60 patients in the treatment group with serum BDNF examination at baseline will undergo this examination.
AIMS, Abnormal Involuntary Motor Scale; ASEX, Arizona Sexual Experience; BARS, Barnes Akathisia Rating Scale; BDNF, brain-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor; MCCB, MATRICS consensus cognitive battery; PANSS, Positive and Negative Syndrome Scale; PASAT, paced auditory serial addition test; PSP, personal and social performance; SAS, Simpson-Angus Scale.

Safety and surveillance

Safety indicators include the following: (1) incidence of adverse events (AEs); (2) changes in body weight, body mass index, blood glucose level and blood lipid profile in the treatment group at baseline; (3) changes in serum prolactin levels in the treatment group; (4) ASEX score in the treatment group; (5) routine blood and urine test results, hepatic and renal function test results and vital signs and 12-lead ECG findings of the treatment group; (6) AIMS/BARS/SAS scores in the treatment group.

All AEs will be immediately added to medical records and case report forms (CRFs). A severe AE is defined as an event occurred in the course of the clinical trial that leads to inpatient treatment requirements, prolonged hospital stay, living and working disabilities, death, life-threatening conditions or birth defects, etc. A new (unexpected) adverse reaction of the drug is defined as an adverse reaction not specified in the package insert. The correlation between AEs and blonanserin treatment will be assessed by the investigators.
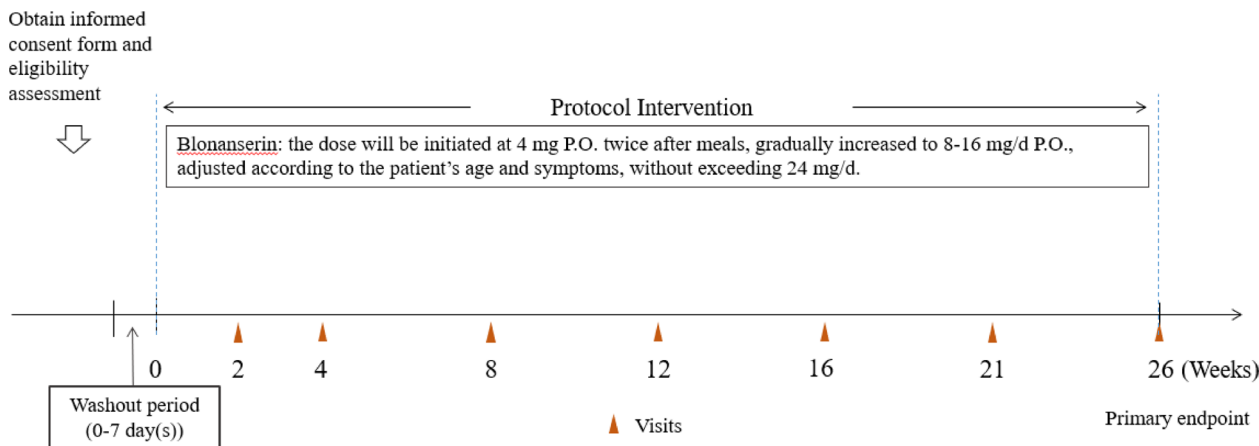
Figure 1 Study flow diagram.

In the treatment of acute phase (first 8 weeks), combined usages of haloperidol injection and olanzapine orally disintegrating tablets will be permitted if the investigators decide that the efficacy of blonanserin monotherapy after 2 weeks is clinically insufficient.

Analysis sets

The full analysis set (FAS) refers to the set of data of all included patients who have used blonanserin at least once. When the primary efficacy indicator is missing, the last observation will be carried forward to the Intention to Treat analysis (ITT analysis) set. The FAS is the primary analysis set. Secondary efficacy indicators will be analysed based on actual data in the FAS.

The per protocol set (PPS) is defined as the set of data of all patients who are fully compliant with the protocol. Such compliance includes the treatment receiving, the data availability of the primary endpoint indicator and no violations against the protocol. The PPS will be used to analyse the primary efficacy indicator.

The safety set (SS) refers to the data set of actually recorded post-treatment safety indicators of patients who have received at least one treatment. The number of SS cases will be used as the denominator for calculating the incidence of adverse reactions.

Data management

Data Analysis System (DAS) for 'Electronic Data Capture (EDC) (V.6.0 or above; Beijing Biovoice Technology Co.) will be used for electronic data management. Electronic CRF (eCRF) will be generated by data managers and verified based on the data verification plan. According to eCRF filling instructions, the data entry staffs will input data into the EDC timely. The CRA will check the consistency of eCRF and source data. When queries are raised, the investigators will answer them in a timely manner. The data manager and the CRA will be responsible to reply to queries and, if necessary, requery them until data are confirmed. After data entry and source data verification, the investigators will sign electronically for confirmation. If data revision is needed after signature signing, resigning is required. The database will be locked up by

the data manager after the database lock record is signed by principal investigator, sponsor, statistical analyst and data manager. Data manager will then submit the database to the statistician. AEs will be coded by the MedDRA (V.20.0 or above) dictionary, and concomitant medications will be classified by WHO ATC.

Statistical analysis

SAS V.9.4 (SAS Institute, USA) will be used for data analysis. Primary efficacy indicator data in PPS and FAS will be analysed simultaneously and data in SS will be analysed for safety evaluation. Student's paired t-test will be used to analyse differences in PSP scores, MCCB scores, numbers of correct answers in the PASAT test, completion time by each hand in the GPT, PANSS total scores, PANSS five-factor subscale scores, multimodal MRI data and serum BDNF levels in the treatment group at baseline and corresponding visit. Student's paired t-test will be used to compare the differences in the treatment group before and after blonanserin administration. t-test will also be used to compare baseline multimodal MRI results and serum BDNF levels between the treatment and normal control groups.

Bilateral tests will be used for all statistical tests. $P < 0.05$ is considered statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination procedures of this research.

DISCUSSION

Cognitive impairment is one of the core symptoms of schizophrenia. Many patients still have cognitive impairment even when psychotic symptoms are alleviated or resolved. Cognitive impairment is highly related to socio-functional disability.[4] It has been suggested by previous studies that dopamine D_3 receptors and 5-HT$_{2A}$ receptors may be associated with cognitive function.[5 8] Blonanserin effectively antagonises dopamine D_3 receptors and the clinical dose of blonanserin can occupy D_3 receptors as

much as D_2 receptors in patients with schizophrenia.[20] Blonanserin inhibits serotonin 5-HT_{2A} receptors but has low affinity for neurotransmitter receptors such as muscarinic M_1, histamine H_1 and adrenergic α_1 receptors,[7] which serve as the basis for improving human cognitive function.

Previous clinical studies in Japan have assessed the improvement of cognitive and social functions in patients with acute schizophrenia who received blonanserin treatment. Results showed that after blonanserin treatment, patients had significantly improved cognitive function, including verbal fluency and executive function, as well as remarkably ameliorated social function, including daily living and work skills. These results together suggest that blonanserin could be effective in improving social and cognitive functions in patients with acute schizophrenia.[10 11] Wang et al[21] carried out a randomised, controlled trial of 75 patients with schizophrenia in China and compared the efficacies of blonanserin and risperidone. According to Sheehan Disability Scale (SDS) results, although both blonanserin and risperidone significantly improved SDS scores in patients with schizophrenia and significantly recovered social function after 8 weeks of treatment, blonanserin showed better efficacy than risperidone. However, existing studies which showed blonanserin could improve social and cognitive functions in patients with schizophrenia had small sample sizes and short observation time period. The current treatment goal for patients with schizophrenia is 'recovery', which includes the improvements of both clinical symptoms and also psychological and social behaviours.[22] Recoveries of cognitive and social functions are especially critical in patients with first-episode schizophrenia wishing to return to normal life as early as possible and to improve their life qualities. Previous clinical studies have demonstrated that blonanserin can alleviate schizophrenia symptoms. In patients with schizophrenia, blonanserin brought remarkable clinical benefits in improving social and cognitive functions. Blonanserin may be a favourable option for long-term administration, as a previous study suggested that long-term treatment with an antipsychotic dose of blonanserin may be unlikely to lead to dopamine supersensitivity in an animal model.[23] Additionally, blonanserin was favourable for patients with treatment-resistant schizophrenia and dopamine supersensitivity psychosis.[24] Therefore, more participants will be included for a longer observation time in the present study to further assess the effectiveness of blonanserin in improving social and cognitive functions in patients with first-episode schizophrenia. Moreover, changes of brain structure and function in patients with schizophrenia received blonanserin will also be observed in this study based on multimodal MRI to further verify the effectiveness of blonanserin in improving social and cognitive functions.

The current study design has limitations, including the single-arm design. However, several clinical trials showed that blonanserin significantly improved cognitive and social functions in patients with schizophrenia;[10 11 21] on the other hand, no robust evidence is available so far to make an antipsychotics a gold standard treatment for cognitive and social dysfunctions improvement in these patients. The investigators thus decided that it would be a better choice for patient's benefits to not introduce a placebo/positive control group in the design. Blinding and randomisation will not be performed either. Data collected in this study, although with some limitations, will help verify effectiveness and safety of blonanserin for improving social and cognitive functions in patients with first-episode schizophrenia in China.

Ethics and dissemination
The study was approved by the ethics committee of the leading site Peking University Sixth Hospital (No. 2018-18), and all included patients are requested to provide written informed consent before enrolment. The study will be conducted according to the principles of the Declaration of Helsinki and follow the principles for clinical research.

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