

# Minocycline for negative symptoms of schizophrenia and possible mechanistic actions: the BeneMin RCT

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## Scientific summary

### The BeneMin RCT

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# Scientific summary

## Background

Even when treatment is adequate, people with established schizophrenia often have an impaired quality of life, experiencing social isolation, self-neglect, unemployment and reduced activities of daily living. Three factors fairly consistently relate to impaired social functioning: cognitive impairment [intelligence quotient (including lower IQ)], the duration of untreated psychosis (DUP) and negative symptoms. A prolonged DUP is associated with the development of marked negative symptoms. Such findings suggest that active psychosis may reflect a neuropathic process that results in negative symptoms and, thus, in impaired quality of life. This hypothesis is reinforced by evidence of progressive loss of grey matter volume (GMV) in the early 1–5 years of psychosis. This has led to interest in directly targeting neuroprotection in the development of early treatments to prevent negative symptoms and cognitive decline and thus to improve social function and quality of life.

Preclinical reports of the neuroprotective effects of the antibiotic minocycline led us to conduct a clinical trial in early schizophrenia comparing minocycline and matching placebo, added to treatment as usual (TAU). After 1 year, improvement in negative symptoms, but not in positive symptoms, was significantly greater after taking minocycline than after taking placebo. The Efficacy and Mechanism Evaluation programme BeneMin study aimed to replicate the initial clinical benefit and to determine whether or not any benefit could be attributed to neuroprotective, anti-inflammatory or cognitive-enhancing effects of the drug.

## Objectives

The study strategy was to use the recently developed PsyGrid infrastructure for UK-wide clinical and imaging research in first-episode psychosis to achieve the following objectives: (1) to determine whether negative symptoms can be lessened or prevented by minocycline treatment initiated early in the course of schizophrenia and (2) to collect biomarker data to test hypotheses about how minocycline improves negative symptoms. To meet these objectives, we designed the BeneMin study, a 1-year multicentre, double-blind randomised placebo-controlled trial of minocycline versus placebo, added to standard antipsychotic drug (APD), for patients within 5 years of a diagnosis of a schizophrenia-related psychosis. The clinical trial treatment was oral minocycline, 300 mg daily for 12 months, or matching placebo capsules. Based on power calculations, we aimed to recruit 225 participants to achieve 85 completers for each treatment group.

The primary efficacy prediction and the mechanistic hypotheses were:

- Minocycline minimises later negative symptoms when administered during the acute phase of early psychosis.
- Minocycline reduces or prevents the negative symptoms of schizophrenia by:
  - reducing the loss of grey matter associated with early psychosis
  - interfering with inflammatory cytokine production
  - acting on glutamate systems to improve negative symptoms and cognitive function.

The primary clinical outcome was the negative symptom subscale score of the Positive and Negative Syndrome Scale (PANSS). The mechanistic biomarker variables were (1) change in medial prefrontal GMV from magnetic resonance imaging (MRI) scans, (2) circulating cytokine concentrations and (3) working memory performance and functional MRI (fMRI) activations in the frontal cortex. We aimed to relate these measures to changes in negative symptom severity and quality of life. Other clinical ratings were made at all

visits, at months 0 (randomisation), 2, 6, 9 and 12, to establish the time course of any benefit. Mechanistic imaging and cognitive measures were made at the first and last visits, and cytokines were measured in blood samples taken at 0, 2, 6 and 12 months. Participants were followed up 3 months after completing the trial phase with all efficacy assessments to determine whether or not any treatment effects had been sustained.

## Methods

The study population was people aged 16–35 years who met the *Diagnosics and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), criteria for schizophrenia or schizophreniform or schizo-affective psychosis, as assessed by the clinical team and confirmed by the Mini-International Neuropsychiatric Interview, which was administered by a member of the research team. Other inclusion criteria included being within 5 years of the onset of psychotic symptoms; the current presence of at least one of four items from the PANSS positive symptom subscale, indicating a continuing episode; being under the care of an early intervention, community or inpatient adult service; and having the ability to provide informed consent, including being fluent in English and having an IQ of > 70. Patients could not take part if, in the investigators' opinion, substance misuse could interfere with the study or if their behaviour involved risk of violence or of self-harm, or if they had coexisting medical disorders revealed at clinical examination or by laboratory blood screening tests.

The primary clinical outcome variable was the negative symptom subscale score on the PANSS. Raters were trained and tested on the Standardised Clinical Interview for PANSS ratings (SCI-PANSS). The PANSS total and positive symptom subscales scores were secondary symptomatic efficacy variables. Functional outcome was assessed by the Global Assessment of Functioning (GAF) scale from the DSM-IV and the self-rated Social Functioning Scale (SFS). Cognitive outcomes included digit-symbol processing speed task, list learning, verbal fluency and IQ measures. Standard clinical measures of APD side effects covered extrapyramidal symptoms (EPS) such as parkinsonism, akathisia and tardive dyskinesias as well as non-neurological APD side effects. Spontaneously reported side effects were recorded. Treatment-emergent depressive symptoms and body mass index (BMI) were monitored.

The three primary biomarker outcome variables tested the three mechanistic hypotheses: (1) preservation of prefrontal GMV, (2) decreased circulating cytokine interleukin (IL) 6 and high-sensitive C-reactive protein (hsCRP) concentrations, and (3) increased dorsolateral prefrontal cortex blood oxygen level-dependent (BOLD) response and performance during the N-back task.

Patients were randomised by the automated Open Clinical Data Management System to receive minocycline increasing from 200 mg to 300 mg/day or matching placebo capsules after they had completed safety and all research assessments. Efficacy measures were repeated at 2, 6 and 9 months, and all safety and research assessments were repeated at 12 months, the end of the trial medication phase. All assessments were repeated at 15 months, which was 3 months after stopping trial medication, to determine whether or not any treatment effects required continuing treatment with minocycline.

## Results

A total of 207 patients were randomised in the trial: 104 to placebo and 103 to minocycline. A total of 75% of the participants remained in the study at 6 months and 60% remained at 12 months. There were no statistically significant treatment effects on any of the primary or secondary clinical or mechanistic outcomes (*Table a*). There was no significant tendency to loss of grey matter or increasing negative symptoms. Patients were not selected for the presence of negative symptoms and their initial ratings corresponded to a mild to moderate degree of severity, which improved minimally over the 12-month treatment phase by < 3 points. Circulating hsCRP and IL-6 cytokine concentrations did not change from

**TABLE a** Summary of best estimates of treatment effect

Primary outcome	Estimate	Standard error	p-value	95% confidence interval
Negative symptoms <sup>a</sup>	-0.19	0.53	0.73	-1.23 to 0.85
<b>Clinical outcomes</b>				
Positive symptoms <sup>a</sup>	-0.19	0.47	0.68	-1.12 to 0.73
Total symptoms (PANSS) <sup>a</sup>	-0.58	1.62	0.72	-3.75 to 2.59
CDSS <sup>a</sup>	-0.06	0.40	0.88	-0.84 to 0.72
GAF score <sup>a</sup>	2.71	2.15	0.21	-1.57 to 6.98
SFS withdrawal <sup>b</sup>	-0.24	0.40	0.55	-1.33 to 0.55
SFS relations <sup>b</sup>	-0.02	0.27	0.94	-0.55 to 0.51
SFS independence-performance <sup>b</sup>	-0.78	0.89	0.38	-2.53 to 0.97
SFS recreation <sup>b</sup>	-0.91	0.89	0.30	-2.65 to 0.82
SFS prosocial <sup>b</sup>	0.19	1.24	0.88	-2.25 to 2.62
SFS independence-competent <sup>b</sup>	-0.49	0.67	0.46	-1.79 to 0.81
SFS employment <sup>b</sup>	-0.12	0.43	0.78	-0.95 to 0.71
Processing speed <sup>c</sup>	-2.14	2.26	0.35	-6.63 to 2.35
Current IQ <sup>c</sup>	-0.56	1.53	0.72	-3.59 to 2.47
Weight <sup>c</sup>	2.71	2.15	0.21	-1.57 to 6.98
<b>Biomarker outcomes</b>				
GMV (left) <sup>c</sup>	-0.09	0.11	0.40	-0.30 to 0.12
GMV (right) <sup>c</sup>	-0.07	0.07	0.34	-0.21 to 0.08
N-back 1 + 2 > 0-back (%BOLD) <sup>c</sup>	-0.66	0.43	0.13	-1.53 to 0.20
IL-6 <sup>b</sup>	0.07	0.10	0.46	-0.12 to 0.26
hsCRP <sup>b</sup>	1.72	1.60	0.28	-1.42 to 4.85
CDSS, Calgary Depression Scale for Schizophrenia. a 2-, 6-, 9- and 12-month follow-up. b 6- and 12-month follow-up. c 12-month follow-up.				

baseline to 6 or 12 months and were unaffected by allocation to minocycline. Treatment effects were not modified in participants with baseline hsCRP and IL-6 concentrations above or below the median.

The pattern of usual drug treatment was unaffected by treatment allocation, and there were no effects on the low rates of EPS or other antipsychotic side effects including the small increase in BMI.

Adherence to trial medication was assessed using self-ratings of attitude to trial medication at every visit. The number reporting a high level of medication adherence (defined by a score of 6 or 7 on the 7-point treatment adherence scale) declined from approximately 85% at 2 months to 65% at 6 months and onwards. This was broadly in line with the rate of non-detectable minocycline measured in an ad hoc assay of minocycline in blood samples taken for cytokines at 6 and 12 months. An exploratory analysis did not reveal significant effects of minocycline in those patients reporting high medication adherence or in those with detectable plasma minocycline.

## Conclusions

The evidence from this study suggests that the administration of minocycline treatment for 1 year, in addition to standard treatment, early in the course of schizophrenia has neither a beneficial nor an adverse effect on clinical outcome. There were no differences in any of the primary or secondary efficacy or mechanistic outcome measures after 2, 6, 9 or 12 months between the minocycline- and placebo- treated groups. There was no evidence of an active process of grey matter loss, cognitive impairment or systemic inflammation that could have been engaged by minocycline. The findings were consistent across centres and unrelated to measures of treatment adherence. The results indicate that minocycline is not an effective adjunct to standard treatment of recent-onset schizophrenia. They also suggest that persistent inflammation and changes in grey matter are not a general or persistent feature in the first 5 years of psychosis.

## Trial registration

This trial is registered as ISRCTN49141214.

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