Clinical Study Report

Effects of add-on Celecoxib treatment in patients with schizophrenia spectrum disorders and inflammatory cytokine profile (TargetFlame)

A multicentre, randomized, double-blind, placebo-controlled, parallel group interventional phase III clinical trial

Investigational Medicinal Product:
Celecoxib

Study Code: TargetFlame

EudraCT Number: 2021-002572-39

First Patient First Visit: 29.07.2022 **– Last Patient Last Visit:** 08.01.2025

Sponsor
Bezirkskliniken Schwaben
vertreten durch
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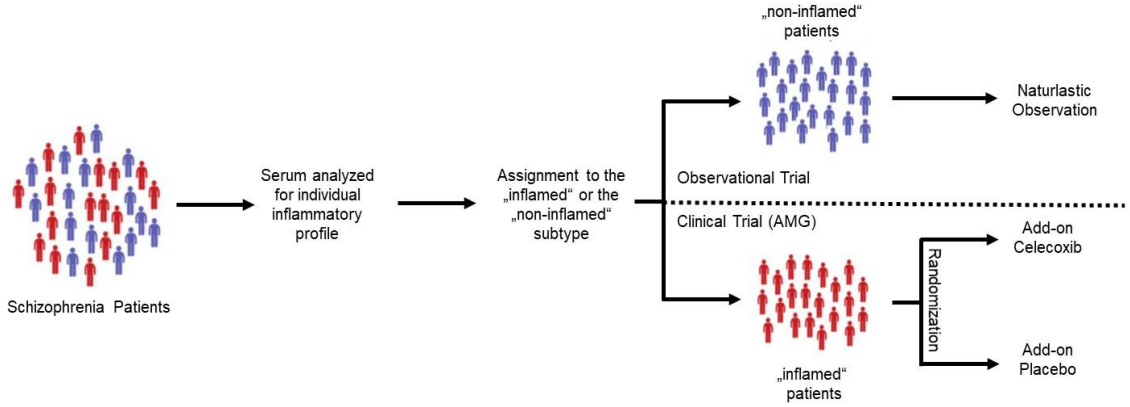
Synopsis

1.	**Sponsor:** Bezirkskliniken Schwaben – vertreten durch Stefan Brunhuber (Chief Executive Officer) Geschwister-Schönert-Straße 4, 86156 Augsburg **Sponsor Delegated Person (SDP):** Prof. Dr. med. Alkomiet Hasan
2.	**Name of Finished Product:** Celecoxib
3.	**Name of Active Ingredient:** Celecoxib
4.	**Individual Study Table:** (only required for submissions) NAP
5.	**Study Title:** Effects of add-on Celecoxib treatment in patients with schizophrenia spectrum disorders and inflammatory cytokine profile (TargetFlame)
	Study Design: A multicentre, randomized, double-blind, placebo-controlled, parallel group interventional clinical trial.
	Study (Protocol) Code Number: TargetFlame
	Eudra-CT Number: 2021-002572-39
6.	**Investigators:** # 1: Prof. Dr. med. Alkomiet Hasan # 2: Dr. med. Joanna Moussiopoulou
7.	**Participating Clinical Trial Sites:** # 1: Bezirkskrankenhaus Augsburg, Klinik für Psychiatrie, Psychotherapie und Psychosomatik der Universität Augsburg Geschwister-Schönert-Straße 1 86156 Augsburg # 2: Klinik für Psychiatrie und Psychotherapie, LMU Klinikum München Nußbaumstraße 7 80336 München
8.	**Publication:** Strube W. et al. Effects of add-on Celecoxib treatment on patients with schizophrenia spectrum disorders and inflammatory cytokine profile trial (TargetFlame): study design and methodology of a multicentre randomized, placebo-controlled trial. J Neural Transm (Vienna). 2023 Aug;130(8):1039-1048. doi: 10.1007/s00702-022-02566-6.
9.	**Study period:** First patient first visit: 29.07.2022; last patient included: 14.11.2024; last patient last visit: 08.01.2025.
	Approvals and Amendments: **First Submission:** Approval: Bundesinstitut für Arzneimittel und Medizinprodukte（BfArM): 16.03.2022; Ethics Committee (EC): 30.03.2022; clinical study protocol (CSP) Version 2.0 28.02.2022 **Amendment 1**: The following major changes were included in AM 1: The CSP was adapted due to further development of the algorithm for differentiation between inflamed/non-inflamed patients; change of investigator at trial site #2. Approval AM1: BfArM: 20.09.2023; EC: 15.09.2023; CSP Version 2.1 04.09.2023

	Amendment 2: The following major changes were included in AM 2: Deletion of follow-up visits (V4 and V5) post intervention. Approval AM2: BfArM: 11.12.2024; EC: 02.12.2024, CSP Version 3.0, 20.11.2024
10.	**Phase of development:** Phase III
11.	**Objectives:** **Primary Objective:** To investigate improvements in psychopathology in patients with schizophrenia spectrum disorders having an inflammatory blood profile randomized to either Celecoxib or placebo. **Secondary Objectives:** include differences in side effects, symptom severity, safety measures and cognitive functions.
12.	**Background/Methodology:** Schizophrenia is a broad clinical entity characterized by different subjective symptoms, behavioural signs, and disease course. Research has pointed to numerous biological indicators tentatively associated with neurocognitive dysfunction, brain structural alterations and neurochemical abnormalities. There is ample evidence that immune dysfunction, and more specifically inflammation, is associated with schizophrenia. If inflammation contributes to symptoms in schizophrenia, treatments with add-on anti-inflammatory drugs should improve clinical outcome. Our goal was to demonstrate the clinical benefit of add-on treatment with the anti-inflammatory drug Celecoxib in a subset of schizophrenia spectrum disorder patients exhibiting an “inflamed” blood profile (pro-inflammatory phenotype). Blood was drawn and corresponding serum samples assessed for levels of several pro-inflammatory cytokines. Patients with a pro-inflammatory phenotype (defined in the text as “inflamed”) were randomized into two arms, either treated with add-on Celecoxib or add-on placebo, and clinically assessed and sampled at baseline and at V3 after 2 months (stratified allocation to the trial). The clinical trial is registered at the EU Clinical Trials Register and DRKS - Deutsches Register Klinischer Studien (identifier: DRKS00029044). Figure 1 displays main aspects of the trial design including the patient flow.  **Figure 1:** Schematic representation of the patient flow. Only patients with an “inflamed profile” will enter the randomized-controlled part of the study. Not all the cytokines will be used for profiling. “Inflamed” is defined as situation with pro-inflammatory cytokine profiling.
13.	**Sample size (planned/analysed):** Planned: To be assessed for eligibility: n = 199 patients To be assessed as “inflamed”: n = 109 patients To be analysed at 2 months (PP): n = 76 (n = 38 in each study group) Patients who have a “non-inflamed” profile will not be randomized but will be invited to serve as a naturalistic control group.

	Analysed: Intent-to-Treat (ITT) population: 30 randomized patients who received investigational medicinal product (IMP) at least once Safety population (SP): 30 patients of the ITT population Per-protocol (PP) population: 22 patients
14.	**Patient Population (Diagnosis):** ICD10: F20 Gender: both male and female Minimum age: 18 years; maximum age: 65 years These definitions were applied for all analysis populations, ITT, SP and PP.
	Main criteria for inclusion: • A DSM-V diagnosis of schizophrenia or schizophrenia-spectrum disorder • PANSS total ≥ 55 at screening • An "inflamed" peripheral profile (see definition below) • Exclusion of a yet non-detected rheumatological or HBV/HCV disease following the screening defined in this protocol • Any antipsychotic treatment being stable for one week prior to inclusion • Inpatients and outpatients • Age between 18 and 65 years • Written informed consent obtained from the participant prior to performing any protocol-related procedures, including screening evaluations • Female participants with reproductive potential must have a negative pregnancy test using a pregnancy test strip as part of the screening visit • Female participants with an inflamed profile and reproductive potential must have a negative serum pregnancy test within seven days prior to randomization • Male participants and female participants who are not capable of bearing children or who use a method of contraception that is medically approved by the health authority of the respective country at screening.
	Main criteria for exclusion: • Patients who are unable to give informed consent • Coercive treatment or forced placement in a psychiatric hospital at the time of study inclusion • Patients who have acute suicidal ideations according to the clinical standard assessment • Medical history of an immune-mediated brain disorder • Chronic use of glucocorticosteroids (temporary use is permitted, if stopped at least 1 month before start of treatment trial) • Chronic use of non-steroidal anti-inflammatory drugs (temporary use is permitted, if stopped at least 1 month before start of treatment trial; on-demand use is permitted only as topic application) • Current use of statins or other lipid-lowering drugs • Current use of tacrolimus or fluconazole • Current use of antihypertensives from the substance class of ACE inhibitors or AT-II antagonists or beta-blockers with the exception of propranolol • Current use of diuretics • Current use of carbamazepine • Chronic use of antiplatelet agents (e.g. ASS, clopidogrel), Phenprocoumon or Non-vitamin K Antagonist Oral anticoagulants (NOAK) • Known history of treatment-resistant hypertension • Known history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease • Known history of congestive heart failure (NYHA II-IV) or current use of digoxin;

	• Known history of type 2 diabetes mellitus • Severe liver disorder(s) (serum albumin <25 g/l or Child-Pugh score >10) • Severe kidney disorder(s) (estimated creatinine clearance <30 ml/min) • Known history of systemic dermatological disorders • Known history of ulcer disease or gastrointestinal (GI) bleeding • Known history of inflammatory bowel disease • Pregnancy or breast-feeding • For male participants: Pregnancy or breast-feeding of the partner • Intolerance to one of the study drugs • Known hypersensitivity to sulphonamides • Known history of asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergictype reactions after taking acetylsalicylic acid(aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 (cyclooxygenase-2) inhibitors • Known history of hereditary Galactose-intolerance, complete Lactase-deficiency or Glucose-Galactose-malabsorption disorder • Concurrent enrolment in another clinical trial where the participant is receiving an IMP or participation in another clinical trial with IMP during the last 30 days before inclusion or 7 half-lives of previously used IMP, whichever is longer.
15.	**Test product, dose and mode of administration:** **Experimental intervention**: Application of double-blind add-on Celecoxib at a dosage of 400 mg/day (morning: 200 mg; evening: 200 mg) before meals (group 1) **Control intervention**: Application of double-blind add-on placebo (morning and evening) before meals (group 2) **Batch-No. (Ch.-B):** TF/202219, TF/202310, TF/202350, TF/202437
16.	**Duration of administration:** Maximum of 56 days (V1-V3)
17.	**Background therapy:** Standard of care **Comparator**: NAP
	Blinding: Double-blind
18.	**Criteria for evaluation:** **Primary endpoint:** Change in symptom severity in randomized patients following treatment with add-on Celecoxib compared to control patients following treatment with add-on placebo as assessed by total PANSS score changes from baseline to two months (56 days) after treatment initiation. **Secondary endpoints:** • Disease severity in the positive, negative, and general psychopathology dimensions assessed using the P-PANSS, N-PANSS and GP-PANSS subscale scores after two months compared to baseline. • Change in total PANSS score after two months compared to baseline. • Andreasen Remission criteria after two months compared to baseline. • Global Assessment of Functioning scale (GAF) score after two months compared to baseline).
	Efficacy: Efficacy assessments follow endpoint analyses.
	Safety assessments: Safety was assessed from the start of the intervention until V3 (56 days after the last intervention). An independent Safety Monitoring Board supported review of safety data and trial progress.

19.	**Statistical methods:** Statistical analyses were determined and prespecified prior to unblinding in a statistical analysis plan (SAP). An interim analysis was not planned and not conducted. The statistician remained blinded until data-base hard-lock. Descriptive statistics will be provided for all data separated by treatment group, by visit and by enrolment centre. Mean, median, standard deviation, range, interquartile range, and number of observations will describe continuous variables. Absolute and relative frequencies will describe categorical variables. All statistical tests will be carried out two-tailed; the alpha (level of significance) is 5%. The randomization procedure will be evaluated by a comparison of the two treatment groups for all relevant variables recorded at baseline. Available data of patients with a non-inflamed profile will be compared to those with an inflamed profile at baseline as an exploratory analysis. Outcomes will be reported as suggested by the CONSORT statement. Population for analysis *Intention-to-Treat (ITT) Population:* All randomized patients who received at least one dose of IMP *Per-protocol Population (PP):* All randomized patients evaluable for the primary endpoint without major protocol deviations *Safety population (SP):* The safety analysis set consists of all patients who entered the trial and was used for conducting all safety analyses (corresponds to the ITT population) Study groups Group 1: 56 days Celecoxib (twice daily 200 mg) Group 2: 56 days placebo pill (twice daily) First analyses: For continuous primary and secondary endpoints the assumption of normal distribution was checked using the Kolmogorov-Smirnov test and the assumption of homogeneity of variance was checked using Levene's test for homogeneity of variance. As these assumptions were partly violated, in such cases non-parametric tests were used for analysis of group and time differences. For analysis of time x group interactions suitable nonparametric tests are available. Thus, exploratively, for time x group interactions linear mixed model (LMM) was applied, as LMM is relatively robust against violations of normality and variance inhomogeneity assumption, and therefore LMM results still provide evidence about time x group interaction. Furthermore, LMM were adjusted for intervening variables site, gender, algorithm, age and BMI while for nonparametric tests it was not possible to account for these intervening variables adequately. Primary endpoint analysis: The primary endpoint (Baseline V1 vs. V3) was performed on the ITT population. For the primary endpoint, exploratively a linear mixed model was performed intending to analyse group x time interactions. For this analysis, baseline differences in PANSS total scores were compared using Mann-Whitney-U-Tests. In cases of significant baseline group differences, follow-up values were normalized to baseline. LMM analyses were adjusted for centre, BMI, age and gender (as obesity, age and gender may impact cytokine levels). Additionally, analyses were adjusted for the version of the used algorithm (v1, v2) since the probably higher rate of inflamed patients for the v2 algorithm might be a source of bias. Furthermore, as significant deviations from normality and variance homogeneity assumption were detected, group differences were analysed with Mann-Whitney-U-Tests, and time differences within groups were analysed with Wilcoxon tests. Secondary endpoint analysis: If requirements for parametric tests were met, LMM adjusted for age, BMI, gender, version of algorithm and, if necessary, for related baseline values were calculated. In cases where the assumptions of normality or variance homogeneity were violated, a monotonic continuous transformation of variables was performed. If this first step was not successful, corresponding non-parametric tests (Mann-Whitney U-test for group differences, Wilcoxon tests for time differences within groups) were computed. If requirements for parametric tests were not met, exploratively a LMM as specified above was additionally calculated.

Additionally, binary logistic regression analysis including a factor variable for centres was performed. Side-effects, AE and SAE were analysed with descriptive statistics and likelihood-ratio tests and Fisher´s Exact test where necessary. Demographic information are shown for each group separately. Dichotomous variables were analysed with likelihood-ratio tests and continuous variables were analysed using analyses of variance or respective non-parametric tests. All tests of secondary endpoints were computed in the ITT and per protocol (PP) populations in an explorative manner on a two-sided significance level of 5%. Outcome data of inflamed patients who participated in the double-blind treatment phase were compared to the outcome data of the non-inflamed patients (naturalistic control group) in an exploratory manner.

20. **Summary - Conclusions:**

Patient demographics and patient disposition

In total 30 inflamed patients were included in the study (FPFV: 29.07.2022; LPLV: 02.12.2024 (LPLV: 08.01.2025 for non-inflamed patient). Eight of 30 patients were excluded from the PP analysis set. Reasons for exclusion were mainly incompliance to IMP intake (R108, R110, R111, R201, R204, R206, R223) or lost to follow-up (R214).

15 patients were included in group 1 (50%), 15 patients in Group 2 (50%).

The study visit V3 was completed by 12/15 (80%) patients in Group 1, and 13/15 (86.7%) patients in Group 2.

Only adults between 18 and 65 years were included. The median age was 35 (23 to 62) years in group 1 (4 male, 11 female), 42 (23 to 64) years in group 2 (8 male, 7 female).

Distributions of relevant demographics at baseline are given in Table 1.

Table 1A (ITT population)

	Celecoxib			Placebo			Chi²	df	p
Site (BKH Augsburg / LMU)	8 / 7			10 / 5			0.556	1	0.456
Algorithm (A1 / A2)	5 / 10			5 / 10			0.000	1	1.000
Gender (male / female)	4 / 11			8 / 7			2.222	1	0.136
	N	mean	sd	N	mean	sd	F	df	p
Age (years) [1)]	15	38.13	10.89	15	41.53	12.90	0.608	1, 28	0.442
BMI	15	29.45	4.66	15	27.66	4.36	1.174	1, 28	0.288

[1)] In the group Celecoxib the median age was 35.0 years (min. 23 years, max. 62 years); in the group Placebo the median age was 42.0 years (min. 23 years, max. 64 years)

Table 1B (Per Protocol population)

	Celecoxib			Placebo			Fisher´s Exact Test		
Site (BKH Augsburg / LMU)	6 / 5			9 /3			0.400		
Algorithm (A1 / A2)	5 / 6			4 / 8			0.680		
Gender (male / female)	4 / 7			7 / 5			0.414		
	N	mean	sd	N	mean	sd	F	df	p
Age (years) [2)]	11	39.55	11.07	12	41.58	12.67	0.167	1, 21	0.687
BMI	11	29.68	4.061	12	27.40	4.640	1.562	1, 21	0.225

[2)] In the group Celecoxib the median age was 41.0 years (min. 26 years, max. 62 years); in the group Placebo the median age was 42.0 years (min. 26 years, max. 64 years)

Table 1: Relevant demographic variables in all two study groups. A: ITT Population, B: PP Population. Legend: BKH, Bezirkskrankenhaus; LMU, Ludwig Maximilians University; BMI, Body Mass Index; N, group size; sd, standard deviation; min, minimum; max, maximum; df, degrees of freedom, p, p-value; F, F statistic

More than 1000 patients with schizophrenia were screened for eligibility and from that group 70 patients fulfilled inclusion criteria, had no exclusion criteria and agreed to participate. From that group, 40 were classified as non-inflamed and could not be randomized. In the end, 30 patients could be randomized to either celecoxib or to placebo. Figure 2 shows the CONSORT chart of the trial.

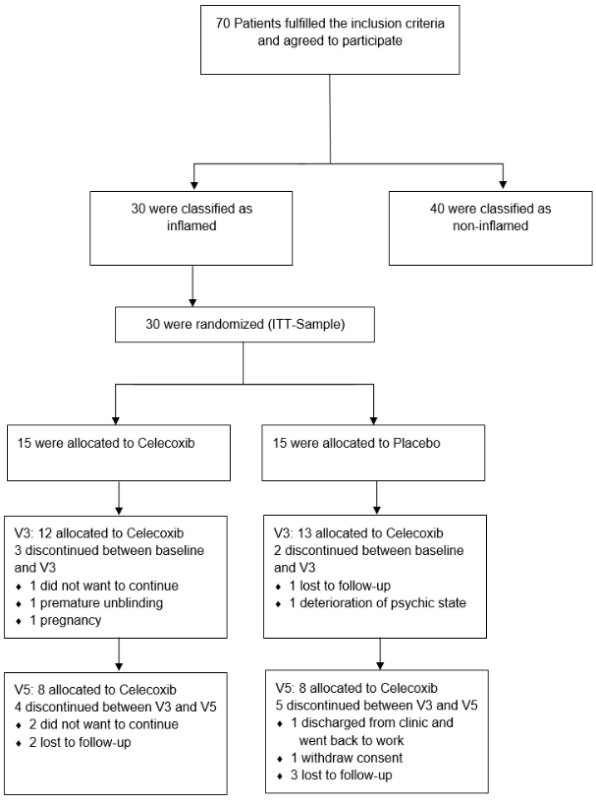


Figure 2: **CONSORT chart. Please see text above for further information.**

Concomitant therapy during the study
All patients received the routine care treatment in the respective participating study centre including pharmacotherapy, psychotherapy, and psychosocial treatments in accordance with the defined inclusion and exclusion criteria.

Medical history and comorbidities
Medical history and comorbidities were assessed as part of the inclusion process. No unexpected findings were observed here. Deviations from the protocol are listed below.

Compliance:

Protocol Deviations (PD):
49 PD were reported in 17/30 patients. Besides the PD which led to the exclusion of the patients (R108, R110, R111, R201, R204, R206, R223) from the PP analysis no further major PD were reported.

Study medication:
All patients of the ITT population received at least one dose of IMP or at least one intervention. 5 patients received IMP but did not reach visit 3. From these 5 patients, 3 were randomized to group 1, and 2 were randomized to group 2. From the 30 randomized patients that received the IMP 15 were randomized to group 1, 15 were randomized to group 2.

Adherence to intervention:
Overall compliance for intervention was good. Patients who were in the trial were very likely to reach primary endpoint as shown in figure 2.

Safety Assessments (all patients included)
Annual Safety Reports have been provided to BfArM and EC for the following periods:
DSUR 1: 16.03.2022 –15.03.2023

DSUR 2: 16.03.2023 –15.03.2024
DSUR 3: 16.03.2024 – 15.03.2025
Adverse Events and one Serious Adverse Event were classified according to CTCAE v5.0; MedDRA Version 27.1. SAE and MedDRA Version 28.0 AE (no change in preferred term).

Safety Results
Safety results are reported in the treatment groups of the actual study treatment, regardless of randomization.

Adverse Events (AE)
A total of 52 AEs were reported in 20 (66,7 %) of 30 patients as detailed in Table 2. 9 (30 %) patients experienced 27 AE in group 1, 11 (36,7% %) patients experienced 25 AE in group 2, (Fisher's Exact Test (two-sided): p = 0.439) as detailed in Table 2**.** Please see appendix for further details.

	Group 1	Group 2	Sum
Patients with AE	9 (30%)	11 (36,67%)	**20 (66,67%)**
Patients without AE	6 (20%)	4 (13,33%)	**10 (33,33%)**
Total	**15 (50%)**	**15 (50%)**	30 (100%)

Table 2: Crosstables for AEs (yes/no) across groups

44 (84,6 %) AEs were rated grade 1 (mild), 8 (15,4 %) grade 2 (moderate), 0 (0 %) grade 3 (severe), 0 (0 %) grade 4 (life-threatening) and 0 (0%) grade 5 (death). AE intensity was not significantly different between the groups (Fisher's Exact Test (two-sided): p = 0.458, see table 3).

	Group 1	Group 2	Sum
Mild	24 (46,15%)	20 (38,46%)	**44 (84,62%)**
Moderate	3 (5,77%)	5 (9,62%)	**8 (15,38%)**
Total	**27 (51,92%)**	**25 (48,08%)**	52 (100%)

Table 3: Crosstables for AE intensity across groups

13 AEs were deemed to be related to celecoxib/placebo as detailed in Table 4 (Fisher's Exact Test (two-sided): p = 0.752).

	Group 1	Group 2	Sum
AE with causal relationship	6 (11,52%)	7 (13,5%)	**13 (25%)**
AE without causal relationship	21 (40,38%)	18 (34,6%)	**39 (75%)**
Total	**27 (51,92%)**	**25 (48,1%)**	52 (100%)

Table 4: Crosstables for AE with/without relationship

Serious AE (SAE)
One SAE was reported in Group 2.

Suspected Serious Adverse Reactions (SAR)
No SAR was reported.

Suspected Unexpected Serious Adverse Reactions (SUSAR)
No SUSAR was reported.

Non-serious Adverse Events (AE)

A total of 51 non-serious AEs in 20 (66,7%) patients were reported during the study. 9 patients in group 1 (30%), 11 patients in group 2 (36,7%), reported AE with no differences in distribution across groups (Fisher´s Exact Test: p = 0.439).

ECG
ECG investigations did show pathologic findings in 3 patients of group Celecoxib and in 2 patients of group 2 that were not related to the intervention (Fisher´s Exact Test (2-sided): p = 1.00.

Efficacy Results

Primary Endpoint

One-sample Kolmogorov-Smirnov test confirmed a normal distribution of the data all p > 0.20, except for Celecoxib, baseline (p = 0.021) and variance homogeneity was confirmed with Levene's test at V1 (p = 0.312), but not at V3 (p = 0.007). Nonparametric Mann-Whitney U-test revealed no significant group differences at baseline (p = 0.305) and at V3 (p = 0.979). Wilcoxon tests resulted in significant PANSS total improvement for Celecoxib (p = 0.045) and for the Placebo group (p = 0.003). The primary endpoint analyses in the ITT-population did not establish a significant time x group interaction for the comparison of the two study groups between V1 and V3 (p = 0.354) and with no significant group differences (p = 0.431), while there were significant time effects (p < 0.0005) and significant gender influences (p = 0.012) (explorative analysis with LMM) (see tables 5a and b, 6 and appendix).

Visit		N	Mean	Median	sd	min, max	range	IQR
baseline	Celecoxib	15	70.20	66.0	14.229	55, 103	48	25
	Placebo	15	72.20	69.0	10.831	56, 97	41	16
	Total	30	71.20	68.0	12.466	55, 103	48	18
v3	Celecoxib	12	65.25	65.0	19.536	43, 104	61	33
	Placebo	13	61.46	61.0	7.612	49, 73	24	14
	Total	25	63.28	62.0	14.409	43, 104	61	18

Table 5a: Descriptive statistics of primary endpoint analyses (ITT population). N, sample size; sd, standard deviation; min, minimum; max, maximum; IQR, interquartile range

controlled for site						controlled for algorithm						controlled for gender					
Visit	group	site	Mean	N	sd	Visit	group	algorithm	Mean	N	sd	Visit			Mean	N	sd
baseline	Celecoxib	BKH Augsburg	70.13	8	16.164	baseline	Celecoxib	A1	72.00	5	18.221	baseline	Celecoxib	male	86.250	4	15.586
		LMU	70.29	7	12.945			A2	69.30	10	12.833			female	64.364	11	8.370
	Placebo	BKH Augsburg	71.80	10	9.750		Placebo	A1	70.60	5	6.348		Placebo	male	75.000	8	11.662
		LMU	73.00	5	13.982			A2	73.00	10	12.745			female	69.000	7	9.626
v3	Celecoxib	BKH Augsburg	63.33	6	14.473	v3	Celecoxib	A1	59.40	5	16.802	v3	Celecoxib	male	75.750	4	24.798
		LMU	67.17	6	24.927			A2	69.43	7	21.509			female	60.000	8	15.547
	Placebo	BKH Augsburg	60.22	9	7.242		Placebo	A1	63.80	5	8.585		Placebo	male	62.857	7	4.880
		LMU	64.25	4	8.770			A2	60.00	8	7.131			female	59.833	6	10.226

Table 6b: Descriptive statistics of primary endpoint analyses (ITT population**), covariates,** N, sample size; sd, standard deviation;

Nonparametric Wilcoxon Test			Nonparametric Mann-Whitney U-Test		
Time (V1/V3)			Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-2.001	0.045	V1	-1.038	0.305
Placebo	-2.944	0.003	V3	-0.027	0.979

Table 6: Statistical Analysis for primary endpoint analysis (nonparametric Wilcoxon and Mann-Whitney U-tests (ITT population) Z statistic; p, p-value

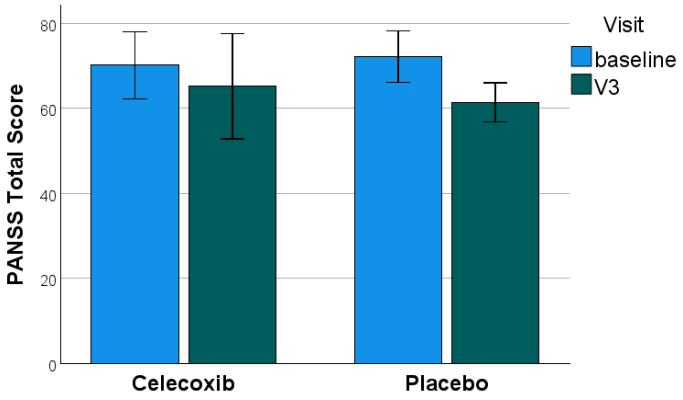


Figure 3: Visualisation of mean PANSS total values. Error bars refer to 95%CI

The same analyses were repeated using the PP population. Here, analyses showed no significant group effects (Mann-Whitney U-test: all p ≥ 0.487), Wilcoxon tests resulted in significant PANSS total improvement for Celecoxib (p = 0.029) and for the Placebo group (p = 0.008); see tables 7 and App.6. Figure 4 shows the visualization of mean PANSS total values in the PP population.

		PANSS total score						
Visit		N	Mean	Median	sd	min, max	range	IQR
baseline	Celecoxib	11	72.18	67.0	14.573	55, 103	48	22
	Placebo	12	71.67	70.0	8.815	56, 89	33	12
	Total	23	71.91	68.0	11.638	55, 103	48	15
v3	Celecoxib	11	63.00	62.0	18.788	43, 104	61	23
	Placebo	11	61.55	61.0	7.528	49, 73	24	13
	Total	22	62.27	61.5	13.987	43, 104	61	19

Table 7: Mean values of primary endpoint analyses (PP population). N, sample size; sd, standard deviation; min, minimum; max, maximum; IQR, interquartile range

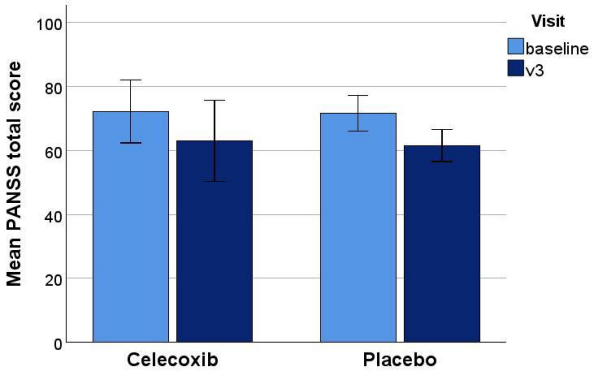


Figure 4: Visualisation of mean PANSS total values in the PP population. Error bars refer to 95%CI

Secondary Endpoints

Secondary Endpoints calculated for V1 vs V3

The following paragraphs describe the analyses for the secondary endpoints for the V1 vs V3 contrasts. Figures show all available data for all performed visits.

PANSS: PANSS positive, PANSS negative, PANSS general and GAF scores were analyzed. As several unspecific time effects without any time x group interaction or main effect of group were observed, we refer to the Appendix tables regarding the detailed test statistics. In short,

for the V1/V3 analyses significant effects were shown for PANSS positive (Celecoxib: p = 0.029, placebo: p = 0.012), PANSS negative (p = 0.004) and PANSS general (p = 0.007). Please see figure 5 for the visualization and tables App.2 to App.4 for statistical analyses.

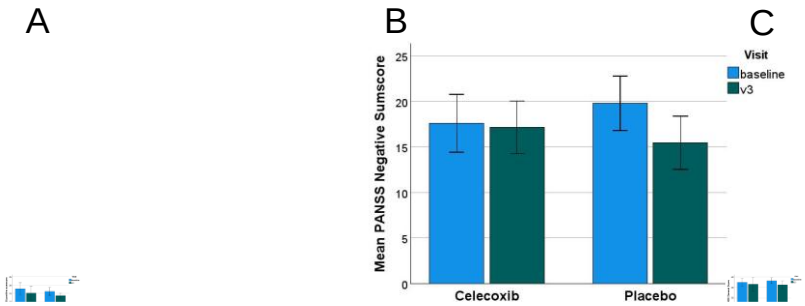


Figure 5: Mean PANSS values for baseline and visit 3. A: PANSS positive, B: PANSS general, C: PANSS negative. Error bars show 95%CI

Figure 6: Mean GAF values for baseline and visit 3. Error bars show 95%CI

GAF: ITT A analyses showed no significant main effects for factors group (Z > -1.31, p > 0.19) or time (Z > -1.89, p > 0.059) or interaction regarding the factors group or time (V1/V3) (explorative; $F_{(1\ ,\ 21.7)}$ = 0.21, p = 0.65). Please see figure 6 for visualization.

The same analyses were repeated for the PP population. For PANSS and GAF we observed no significant group effect (all p > 0.060), improvement for V3 vs. V1 was significant in the Celecoxib group for PANSS total (p = 0.029), PANSS negative (p = 0.025) and GAF (p = 0.008) and in the placebo group for all PANSS sum scores (all p < 0.020).

Andreasen Remission criteria: In both groups none of the patients fulfilled the criteria at baseline. At V3 after 2 months in the Celecoxib group 2 of 12 patients (17%) and in the placebo group 5 of 13 patients (38%) fulfilled the criteria (Fisher´s Exact Test: p = 0.378 (n.s.)).

Binary logistic regression: A binary logistic regression was performed with the dependent variable group and the independent variables PANSS total score, center, gender, time, algorithm, age, and BMI. Only gender (p = 0.007) and BMI (p = 0.022), but not PANSS total (p = 0.408), were identified as significant predictors for group. The proportion of correct classifications increased from 51.3% to 68.4%.

Overall Conclusion:

The clinical trial recruited 30 patients with an inflamed profile.

Reported AE/SAE were in accordance with the known safety profile of the intervention in this patient population and did not show any relationship to our study groups.

	In conclusion, we found no evidence that celecoxib is superior to placebo in improving the condition of patients from the schizophrenia spectrum. It should be noted that the originally planned sample size was not achieved since public funding was terminated prematurely.
21.	**Date of report:** **Date:** 07.01.2026

APPENDIX

Table App.1 – App.10 Detailed secondary outcome analyses:

Table App.1: PANSS total score, Intention-to-treat population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	15	70.20	66.0	14.229	48	25
	Placebo	15	72.20	69.0	10.831	41	16
v3	Celecoxib	12	65.25	65.0	19.536	61	33
	Placebo	13	61.46	61.0	7.612	24	14

LMM (explorative)	df	F	P
Intercept	1, 25.879	14.527	0.001
Visit (Baseline/V3)	1, 23.245	20.782	< 0.0005
Group	1, 24.590	0.641	0.431
Site	1, 23.206	0.081	0.778
Gender	1, 23.188	7.417	0.012
Algorithm	1, 23.148	0.144	0.708
Age	1, 23.301	0.194	0.664
BMI	1, 26.443	0.054	0.819
Visit * Group	1, 23.481	0.894	0.354

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	p		Z	P
Celecoxib	-2.001	0.045	V1	-1.038	0.305
Placebo	-2.944	0.003	V3	-0.027	0.979

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; Z, Z statistic; p, p-value

Table App.2: PANSS positive score, Intention-to-treat population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	15	17.80	17.0	6.505	23	8
	Placebo	15	16.13	18.0	4.454	13	7
v3	Celecoxib	12	15.17	14.0	6.450	18	12
	Placebo	13	13.62	15.5	2.631	10	3

LMM (explorative)	Df	F	P
Intercept	1, 28.398	4.053	0.054
Visit (Baseline/V3)	1, 24.694	16.245	< 0.0005
Group	1, 23.591	1.466	0.238
Site	1, 23.384	0.644	0.430
Gender	1, 23.273	0.604	0.445
Algorithm	1, 23.003	0.039	0.846
Age	1, 23.497	0.293	0.593
BMI	1, 29.471	0.101	0.753
Visit * Group	1, 25.088	0.018	0.894

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-2.182	0.029	V1	-0.291	0.775
Placebo	-2.515	0.012	V3	-0.327	0.769

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; Z, Z statistic; p, p-value

Table App.3: PANSS negative score, Intention-to-treat population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	15	17.60	17.0	5.742	24	8
	Placebo	15	19.80	20.0	5.388	16	10
v3	Celecoxib	12	17.17	15.5	4.529	16	7
	Placebo	13	15.46	15.0	4.841	14	9

Linear mixed model	df	F	P
Intercept	1, 26.042	13.761	0.001
Visit (Baseline/V3)	1, 24.496	9.891	0.004
Group	1, 23.082	0.275	0.605
Site	1, 22.864	2.416	0.134
Gender	1, 22.810	7.309	0.013
Algorithm	1, 22.479	1.474	0.237
Age	1, 23.012	0.143	0.708
BMI	1, 26.368	1.814	0.190
Visit * Group	1, 24.731	2.914	0.100

Legend: N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; p, p-value

Table App.4: PANSS general score, Intention-to-treat population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	15	34.80	33.0	7.093	25	10

	Placebo	15	36.27	36.0	5.189	18	8
v3	Celecoxib	12	32.92	32.0	10.440	34	18
	Placebo	13	32.38	33.0	6.292	23	8

Linear mixed model	df	F	P
Intercept	1, 25.403	7.976	0.009
Visit (Baseline/V3)	1, 23.099	8.697	0.007
Group	1, 25.313	0.039	0.845
Site	1, 23.167	0.140	0.712
Gender	1, 23.145	5.248	0.031
Algorithm	1, 23.129	0.023	0.880
Age	1, 23.234	0.355	0.557
BMI	1, 25.818	0.662	0.423
Visit * Group	1, 23.298	0.350	0.560

Legend:N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; p, p-value

Table App.5: GAF score, Intention-to-treat population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
v1	Celecoxib	14	50.86	51.0	7.645	27	12
	Placebo	14	47.64	51.5	10.987	36	16
v3	Celecoxib	12	55.83	59.0	11.360	37	15
	Placebo	12	50.83	50.5	8.820	32	10

LMM (explorative)	Df	F	P
Intercept	1, 24.854	15.371	0.001
Visit (Baseline/V3)	1, 21.072	6.918	0.016
Group	1, 21.629	0.287	0.598
Site	1, 21.580	0.109	0.745
Gender	1, 21.427	0.000	0.991
Algorithm	1, 21.510	1.068	0.313
Age	1, 21.521	1.222	0.281
BMI	1, 24.175	0.150	0.701
Visit * Group	1, 21.716	0.207	0.654

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-1.887	0.059	V1	-0.461	0.667
Placebo	-1.178	0.239	V3	-1.308	0.198

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; Z, Z statistic; p, p-value

Table App.6: PANSS total score, Per Protocol population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	11	72.18	67.0	14.573	48	22
	Placebo	12	71.67	70.0	8.815	33	12
v3	Celecoxib	11	63.00	62.0	18.788	61	23
	Placebo	11	61.55	61.0	7.528	24	13

LMM (explorative)	df	F	P
Intercept	1, 18.424	9.923	0.005
Visit (Baseline/V3)	1, 20.059	19.747	< 0.0005
Group	1, 17.510	0.887	0.359
Site	1, 16.208	0.351	0.562
Gender	1, 16.176	5.404	0.033
Algorithm	1, 16.192	0.133	0.720
Age	1, 16.350	0.447	0.513
BMI	1, 19.037	0.132	0.720
Visit * Group	1, 20.434	0.100	0.755

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-2.179	0.029	V1	-0.709	0.487
Placebo	-2.652	0.008	V3	-0.362	0.748

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; Z, Z statistic; p, p-value

Table App.7: PANSS positive score, Per Protocol population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	11	17.27	17.0	5.968	21	9
	Placebo	12	16.08	16.5	4.400	13	7
v3	Celecoxib	11	14.27	13.0	5.934	17	11
	Placebo	11	13.82	14.0	2.601	10	3

LMM (explorative)	df	F	P
Intercept	1, 18.187	5.444	0.031
Visit (Baseline/V3)	1, 20.065	12.812	0.002
Group	1, 16.491	2.402	0.140
Site	1, 16.206	4.130	0.059
Gender	1, 15.912	1.450	0.246
Algorithm	1, 15.932	0.053	0.821
Age	1, 16.054	0.331	0.573
BMI	1, 19.076	1.011	0.327

Visit * Group	1, 20.471	0.002	0.966

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-1.940	0.052	V1	-0.309	0.786
Placebo	-2.317	0.020	V3	-0.132	0.898

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; Z, Z statistic; p, p-value

Table App.8: PANSS negative score, Per Protocol population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	11	19.55	20.0	5.165	18	8
	Placebo	12	19.33	20.0	5.158	15	10
v3	Celecoxib	11	16.82	15.0	4.579	16	5
	Placebo	11	15.64	15.0	4.675	14	9

Linear mixed model	df	F	P
Intercept	1, 19.081	6.441	0.020
Visit (Baseline/V3)	1, 20.060	18.418	< 0.0005
Group	1, 16.321	0.225	0.642
Site	1, 16.231	1.279	0.275
Gender	1, 15.899	3.763	0.070
Algorithm	1, 15.912	0.377	0.548
Age	1, 16.106	0.009	0.928
BMI	1, 20.287	0.131	0.721
Visit * Group	1, 20.598	0.216	0.647

Legend: sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; p, p-value

Table App.9: PANSS general score, Per Protocol population

Descriptive Statistics		N	Mean	Median	sd	range	IQR
Baseline	Celecoxib	11	35.36	33.0	7.839	25	13
	Placebo	12	36.25	36.0	3.957	13	7
v3	Celecoxib	11	31.91	32.0	10.319	34	15
	Placebo	11	32.09	33.0	4.763	17	5

Linear mixed model	df	F	P
Intercept	1, 18.097	3.646	0.072
Visit (Baseline/V3)	1, 20.088	8.833	0.008
Group	1, 17.489	0.018	0.895
Site	1, 16.216	0.015	0.904
Gender	1, 16.153	3.644	0.074
Algorithm	1, 16.164	0.136	0.717
Age	1, 16.302	1.411	0.252
BMI	1, 18.634	0.432	0.519

Visit * Group	1, 20.421	0.045	0.834

Legend: sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; p, p-value

Table App.10: GAF score, Per Protocol population

Visit		N	Mean	Median	sd	range	IQR
v1	Celecoxib	10	50.70	51.5	8.642	27	14
	Placebo	11	46.91	51.0	11.802	36	20
v3	Celecoxib	11	57.91	60.0	9.224	30	15
	Placebo	10	49.70	50.0	8.932	30	15

LMM (explorative)	df	F	P
Intercept	1, 18.561	10.309	0.005
Visit (V1/V3)	1, 18.756	6.239	0.022
Group	1, 16.380	1.054	0.320
Site	1, 15.794	0.397	0.538
Gender	1, 15.446	0.383	0.545
Algorithm	1, 15.567	0.300	0.591
Age	1, 15.521	0.948	0.345
BMI	1, 19.113	0.135	0.717
Visit * Group	1, 19.750	0.740	0.400

Nonparametric Wilcoxon Test Time (V1/V3)			Nonparametric Mann-Whitney U-Test Celecoxib vs. Placebo		
	Z	P		Z	P
Celecoxib	-2.688	0.008	V1	-0.600	0.557
Placebo	-0.765	0.444	V3	-1.921	0.061

Legend: LMM, linear mixed model; N, group size; sd, standard deviation; IQR, interquatile range; df, degrees of freedom; F, F statistic; p, p-value

Table App.11: Cumulative Summary Tabulation of all **AEs**

Zeilenbeschriftungen	Anzahl von pt_name
Cardiac disorders	**1**
Bradycardia	1
Ear and labyrinth disorders	**1**
Ear pain	1
Endocrine disorders	**1**
Hyperprolactinaemia	1
Gastrointestinal disorders	**12**
Abdominal discomfort	1
Abdominal pain upper	2
Diarrhoea	1
Dyspepsia	2
Dysphagia	1
Gastrointestinal pain	1
Haematochezia	1
Nausea	2
Salivary hypersecretion	1
General disorders and administration site conditions	**2**
Malaise	1
Sensation of foreign body	1
Infections and infestations	**2**
Nasopharyngitis	1
Pulpitis dental	1
Injury, poisoning and procedural complications	**1**
Muscle strain	1
Investigations	**6**
Electrocardiogram QT prolonged	1
Electrocardiogram T wave inversion	1
Weight increased	4
Metabolism and nutrition disorders	**2**
Vitamin B12 deficiency	1
Vitamin D deficiency	1
Musculoskeletal and connective tissue disorders	**2**
Arthralgia	1
Back pain	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**
Melanocytic naevus	1
Nervous system disorders	**5**
Autonomic nervous system imbalance	1
Dizziness	2
Presyncope	1
Radiculopathy	1
Psychiatric disorders	**10**
Affective disorder	1
Anhedonia	1
Depression	2
Negative symptoms in schizophrenia	1
Restlessness	2
Schizoaffective disorder	1
Schizophrenia	1
Sleep disorder	1
Renal and urinary disorders	**2**
Incontinence	1
Urinary retention	1
Respiratory, thoracic and mediastinal disorders	**2**
Asthma	1
Nasal septum deviation	1
Skin and subcutaneous tissue disorders	**1**
Eczema	1
Surgical and medical procedures	**1**
Tooth extraction	1
Gesamtergebnis	**52**

Table App.12: Cumulative Summary Tabulation of SAE

Cumulative Summary Tabulation of all serious Adverse Events

System Organ Class Preferred Term	**Number of events** **Total up to 15.03.2025**
Psychiatric disorders	**1**
Schizoaffective disorder	1