Improvement of synaptic plasticity and cognitive function in RAS pathway disorders

SynCoRAS

Phase IIa Study

Test product: Lovastatin, Lamotrigine, Placebo

Study Code: SYN-1748-MAL-0030-I

EudraCT Number: 2016-005022-10

First Patient First Visit: 22.03.2019 **– Last Patient Last Visit:** 09.02.2023

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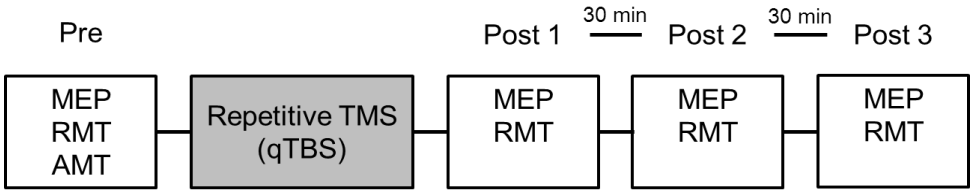
Synopsis

1.	**Sponsor:** Technische Universität München, Fakultät für Medizin, Ismaninger Strasse 22, D- 81675 München, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. med. Volker Mall, Children University Hospital, Social Pediatrics, and Developmental Medicine. Technische Universität München, Heiglhofstraße 65, 81377 München
2.	**Name of Finished Product:** Lovastatin, (Authorisation Number DE/H/4056/001) Lamotrigine (Authorisation Number not available), Placebo (Mannitol/Siliciumdioxid 99.8/0.2)
3.	**Name of Active Ingredient:** Lamotrigin (ATC Code: N03AX09), Lovastatin (ATC Code: C10AA02)
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** Improvement of synaptic plasticity and cognitive function in RAS pathway disorders
	Study Design: Monocentre, randomized, double-blind, parallel-group, placebo controlled, cross-over design (IIT)
	Study (Protocol) Code Number: SYN-1748-MAL-0030-I
	Eudra-CT Number: 2016-005022-10
6.	**Investigator(s):** Prof. Dr. med. Volker Mall, Children University Hospital, Social Pediatrics, and Developmental Medicine. Technische Universität München, Heiglhofstraße 65, 81377 München
7.	**Participating Study Centre:** #1 Children University Hospital, Social Pediatrics, and Developmental Medicine. Technische Universität München, Heiglhofstraße 65, 81377 München The study was planned and conducted as a single-centre study.
8.	**Publication:** not published yet
9.	**Study period:** First patient first visit (FPFV): 22.03.2019; Last patient out: 09.02.2023 The clinical trial was prematurely discontinued on 20.02.2023 due to recruitment problems

	Approvals and Amendments Approval: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM: 09.02.2018.; Ethics Committee (EC): 13.02.2018; Start with CSP Version 2.0 date 16.01.2018 **Amendment 1:** The following major changes were included in AM 1: Changes in the CSP, Extension of visits at intervals. Approval AM1: BfArM: 13.08.2019; EC: 09.09.2019, CSP Version 3.0 AM 1.0 date 16.07.2019 **Amendment 2:** The following major changes were included in AM 2: Extension of the inclusion criteria to include patients age ≥16 years, extension of the timelines, change IMP manufacturer. Approval AM2: BfArM: 16.03.2020; EC: 12.03.2020, CSP Version 4.0 AM 2.0 date 10.01.2020 Note: No patients under the age of 18 were included. **Amendment 3:** The following major changes were included in AM 3: Switch of the order in which experiments I and II are performed in the group of patients suffering from Noonan syndrome (NS). Approval AM1: BfArM: 13.11.2020.; EC: 12.11.2020, CSP 5.0 AM 3.0 date 21.09.2020 Note: No patients were included after Amendment 3. The specially created database to reflect those changes is empty. All data were entered in the original NS and NF databases created at the start of the study.
10.	**Phase of development** Phase IIa
11.	**Objectives:** **Primary Objective:** To investigate if the pharmacological intervention with (a) Lovastatin and (b) Lamotrigine improve synaptic plasticity in patients with Noonan Syndrome and Neurofibromatosis type 1. **Secondary Objectives:** To investigate if the pharmacological intervention with (a) Lovastatin and (b) Lamotrigine improve attentional performance measured by the Test for Attentional Performance (TAP) in patients with Noonan syndrome and Neurofibromatosis type 1. To investigate the differences between Lovastatin and Lamotrigine in improving synaptic plasticity and attentional performance in patients with Noonan Syndrome.
12.	**Methodology:** Learning and attention deficits are very likely to be a clinically relevant problem for each participant with NF1 or NS. Evaluation of these problems and the potentially successful intervention within the trial may have therapeutic consequences for patients. Furthermore, the effect on synaptic plasticity and on attention of the medication (LTG or LOV) is tested placebo-controlled on an individual basis. This information may be important for the initiation of an individual pharmacological treatment.

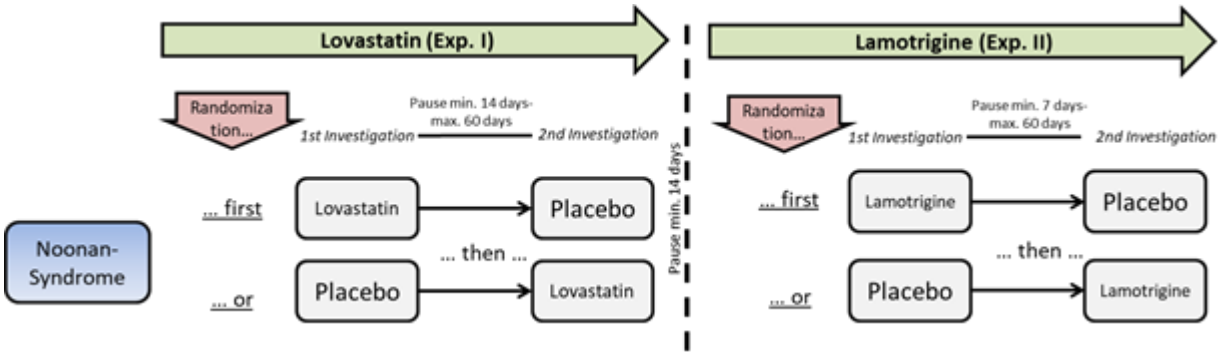
Flow Chart of TMS Investigation:



Timeline of TMS measurements: MEP: motor evoked potential; RMT: resting motor threshold: AMT: active motor threshold; qTBS: quadri-pulse theta burst stimulation.

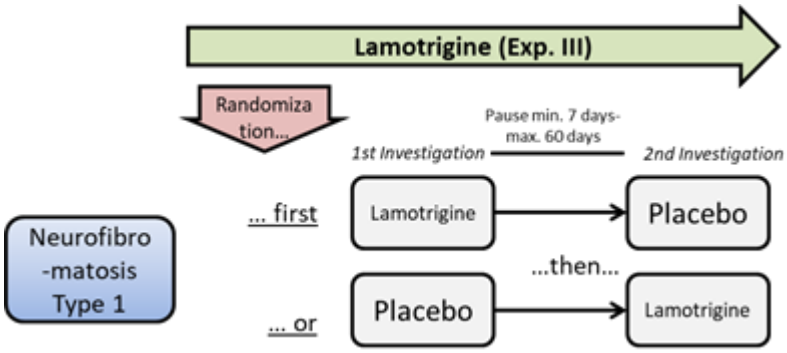
Flow Chart of study drugs

Group 1 (Noonan Syndrome):



Note that the order of Exp. I and Exp. II was switched in CSP version 5.0 AM 3.0 from 21.09.2020; however, no patients were included in the Noonan Syndrome group after this point.

Group 2 (Neurofibromatosis type 1):



13. **Sample size (planned/analysed):**

The sample size estimation revealed that twelve patients per disease entity would be enough to provide appropriate power to all planned primary endpoint tests (two-sided paired samples t-tests) with a global significance level of 5% and adjusted local significance levels using the Bonferroni-Holm procedure. In order to account for some unobtainable data, the sample size was set to 14 patients per group:

To be assessed for eligibility (n = 32)
To be allocated to trial (n = 30)

	To be analyzed (n = 28, 14 in each of the NS and NF1 groups) The actual number of recruited patients was four in the NS group 12 in the NF1 group.
14.	**Patient Population (Diagnosis):** **ICD: Noonan Syndrome (Q87.1) and Neurofibromatosis Type I (Q85.0)** **Gender:** Both, male and female **Age >18 years** up to the CSP version 3.0 AM 1.0 date 16.07.2019 **/** from the CSP version 4.0 AM 2.0 date 10.01.2020 **Age ≥16 years** (no patients under 18 years of age were recruited).
	Main criteria for inclusion 1. Group 1: NS, Group 2: NF1 (both genetically assured) 2. **Age >18 years** up to the CSP version 3.0 AM 1.0 date 16.07.2019 **/** from the CSP version 4.0 AM 2.0 date 10.01.2020 **Age ≥16 years** 3. The adolescent (≥16) and legal guardian who are capable to give their consent and understand the aim and rationale of the study. In case of doubts, an independent medical practitioner will evaluate the capacity to consent. 4. Signed informed consent if ≥ 16 years and legal guardian. 5. Persons who are ≥ 18 years old and capable to give their consent and understand the aim and rationale of the study. In case of doubts, an independent medical practitioner will evaluate the capacity to consent. 6. Signed informed consent if ≥ 18 years. 7. 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. **Main exclusion criteria:** 1. Epilepsy 2. Medication with known CNS effects 3. Severe mental retardation 4. Side effects during previous medication with and contraindications to LTG and/or LOV and/or TMS 5. Psychiatric diseases 6. Previous history of allergic reactions with LTG and LOV medications 7. Potentially unreliable patients 8. Patients who are not suitable for the study in the opinion of the investigator 9. Pregnancy (incl. positive urine pregnancy test) 10. Persons who are incapable of giving consent or do not understand the aim or rationale of the study.
15.	**Test product, dose and mode of administration** **Test product:** Lovastatin, Lamotrigine, LOV-Placebo, LTG-Placebo (Mannitol/Siliciumdioxid 99.8/0.2 %)

	Dose: Group 1 (Noonan Syndrome): Exp. I: **200 mg LOV** daily for four days / LOV-placebo Exp. II: **300 mg LTG** single dose / LTG-placebo Note that the order of Exp. I and Exp. II was switched in CSP version 5.0 AM 3.0 from 21.09.2020; however, no patients were included in the Noonan Syndrome group after this point. Group 2 (Neurofibromatosis type 1): Exp. III: 300 mg LTG single dose / LTG-placebo **TMS** to be performed 2 hours after intake of LTG/LTG-placebo and 4 days after intake of LOV/LOV-placebo. **Method of administration:** Oral use **Batch-No. (Ch.-B):** 1. Batch: LAMO/201904, LOVA/201904 2. Batch: LAMO/202013, LOVA/202004 3. Batch: LAMO/202109, LOVA/202109 4. Batch: LAMO/202208, LOVA/202208
16.	**Duration of administration** Group 1: up to the CSP Version 4.0 AM 2.0 date 10.01.2020 max. of 157 days from the CSP version 5.0 AM 3.0 date 21.09.2020 max 187 days Group 2: max. 61 days
17.	**Background therapy:** standard of care **Comparator:** Placebo (Mannitol/Siliciumdioxid 99.8/0.2 %)
	Blinding: The study was double blind. All patients, clinicians, and study personnel were blinded to the study treatment until final data base closure.
18.	**Criteria for evaluation:** **Primary endpoint:** The primary endpoint for each experiment is the difference between the amplitude of the motor evoked potential (MEP) elicited with transcranial magnetic stimulation (TMS, measured at three time points after interventional TMS for each investigation) after placebo and after medication (LTG and LOV). **Secondary endpoints:** The secondary endpoints for each experiment are the difference between the neuropsychological testing of attention (TAP) and differences in short interval cortical inhibition (SICI) after placebo and after medication (LTG and LOV).

	Another endpoint is the comparison of LTG and LOV effects on synaptic plasticity and attentional performance in the NS group.
	Efficacy: Efficacy assessments follow endpoint analysis.
	Safety assessments Safety was assessed from the start of the intervention until V6 for NS patients and until V2 for NF1 patients. Safety was to be assessed according to CTCAE 4.03 of the US NCI and coded according to MedDRA Version 22.0 (English). Additionally, EMG activity was monitored during qTBS stimulation.
19.	**Statistical methods:** All statistical analyses were specified prior to unblinding in a statistical analysis plan (SAP). An interim analysis was not done for this study. <u>Population for analysis</u> A separate analysis set is defined for each experiment. All analyses are performed on the full analysis sets (FAS-NS-LOV, FAS-NS-LTG, FAS-NF-LTG), consisting of all patients who delivered a full set of MEP measurements within the corresponding experiment. <u>Primary endpoint analysis:</u> The primary endpoint analyses are performed in three separate testing procedures (see table below). This is justified, as two of the experiments are performed on completely different sets of patients and the two experiments performed on the NS group took place more than 3 months apart, so that any carry-over effects can be ruled out using pharmacokinetic reasoning. The primary endpoint of each experiment in AB/BA cross-over design is analyzed using the paired samples two-sided t-test, comparing the MEP amplitude under verum vs. placebo at the three measurement time points. This is a simple analysis, ignoring any period effects. The global significance level is set to 5%. Since experiments NS-LTG and NS-LOV are done on the same set of patients, the significance level for each of those two experiments is 2.5%. The significance level of experiment NF-LTG is 5%. The local significance level is adjusted using the Bonferroni-Holm procedure as follows for the ordered by p-value tests:

Experiment	Test number (ordered by p-value)	Local significance level
NS-LTG, NS-LOV	1	0.025
NS-LTG, NS-LOV	2	0.013
NS-LTG, NS-LOV	3	0.008
NF-LTG	1	0.050
NF-LTG	2	0.025
NF-LTG	3	0.017

	If a period difference seems present, this will be tested using the independent samples t-test for period differences. Secondary endpoint analysis: Secondary endpoints are analyzed by group, sequence, and visit by reporting the number of valid cases, mean, and standard deviation. Due to the low number of patients recruited in the NS group, statistical tests are only performed on the NF group. Treatment differences are tested using the two-sided paired samples t-test at the 5% significance level. Safety: Adverse events and EMG activity during qTBS simulation were recorded and summarized by treatment period.
20.	**Summary - Conclusions:** **Patient demographics and patient disposition** In total, 16 patients were included in the study (FPFV: 22.03.2019; LPLV: 09.02.2023). The NF group recruited 12 patients, all completing both treatment periods. The NS group recruited 4 patients, and 2 of them were lost to follow-up after the first visit, which means they did not complete the first period. Two patients completed all four treatment periods of the NS-LOV and NS-LTG experiments. Patient disposition is summarized in Appendix Table 1. The majority of the patients were male 10/16 (62.5%). Age ranged between 19 and 53 years. Demographics and baseline characteristics are shown in Appendix Table 2.
	Compliance: There were no violations of inclusion or exclusion criteria. The blind was kept for all participants and study personal until the database was hard-locked. Protocol Violation (PV): In the NF group, two PV were reported in 2/12 patients (17%), both rated as minor (delay in TMS measurement due to electrode replacement). The NS group reported 14 PV in 4/4 patients (100%), all of which were rated as minor (delay of several minutes in TMS measurement, delay in visit schedule, early intake of study medication (NS-LOV)). Study medication: Compliance was high (100%) in patients who took lamotrigine, as this medication was given only once per treatment period. Of the two NS patients who took lovastatin, one took the medication from the last treatment period one day too early (minor PV, as stated above). Adherence to intervention: Overall compliance for intervention was good (see several minor PV). Several TMS measurements were delayed a few minutes due to a change of electrodes. **Safety Assessments** (all patients included) Annual Safety Reports were provided to the Health Authority and Ethics Committee for the periods of

DSUR 1: 10.02.2019-09.02.2020
DSUR 2: 10.02.2020-09.02.2021
DSUR 3: 10.02.2021-09.02.2022
DSUR 4: 10.02.2022-09.02.2023
DSUR 5: 10.02.2023-09.02.2024

Safety Results

No adverse events of any kind were reported throughout the study. No EMG activity was observed during qTBS simulation.

Efficacy Results

Primary Endpoint:

The primary endpoint for each experiment is the difference between the amplitude of the motor evoked potential (MEP) elicited with transcranial magnetic stimulation (TMS, measured at three time points after interventional TMS for each investigation) after placebo and after medication (LTG and LOV).

NF-LTG

The mean difference in MEP amplitude in mV between LTG and placebo was -0.06 ±0.22 at 5 min, -0.18 ±0.30 at 30 min, and -0.43 ±0.37 at 60 min post-stimulation (see also Appendix Table 4 where the individual values are presented by treatment and time point). Differences of mean MEP amplitudes at 5, 30 and 60 min were not statistically significant at the 5% significance level (p-value from the paired samples T-test of 0.640 at 5 min, 0.320 at 30 min, and 0.075 at 60 min). Note, that the difference at 60 min is significant at the 10% significance level. No period differences were observed (see Appendix Table 3).

NS-LOV

All four patients in the NS-LOV experiment were randomized to start with placebo in period 1 and continue with lovastatin in period 2, which is why Appendix Tables 5 and 6 are very similar with identical columns for period 1 in table 5 and placebo in table 6. Since only two patients had a cross-over measurement, no statistical tests were performed. The MEP amplitudes are listed by patient in Appendix Tables 5 and 6 and the cross-over difference is as follows:

Patient number	*Cross-over difference of MEP amplitude*		
	5 min	*30 min*	*60 min*
NS-02	0.04	0.04	0.03
NS-04	0.69	1.85	0.15

NS-LTG

Similarly, to the NS-LOV experiment, in the NS-LTG experiment both patients started with placebo and crossed over to lamotrigine. No statistical tests were calculated for the two patients, but their measurements can be seen listed in Appendix Tables 7 and 8, and the cross-over differences are as follows:

Patient number	*Cross-over difference of MEP amplitude*		
	5 min	*30 min*	*60 min*
NS-02	0.00	0.04	-0.01
NS-04	-0.49	-0.49	-0.36

	Secondary Endpoints: SICI All measurements of short interval cortical inhibition are presented by treatment and group in Appendix Table 10. The observed differences were not statistically significant (tested only in the NF-LTG group) as the variation was high. TAP The observed TAP testing values are summarized in Appendix Table 11. None of the tests in the NF-LTG group were statistically significant. **Further analyses:** TMS parameters Further TMS parameters were recorded in all experiments. Summary statistics of all measurements can be found in Appendix Table 9. Statistical tests were only performed in the NF-LTG group. All RMT measurements were higher under LTG than under placebo treatment. This difference was statistically significant at RMT post 1 (p=0.003), RMT post 2 (p=0.001), and at RMT post 3 (p=0.009) in the NF-LTG group. The intensity to target MEP of 1mV was also higher under LTG treatment than under placebo in all groups. In the NF-LTG group this difference was statistically significant (LTG: 69.7 ±18.6 vs. placebo: 61.6 ±12.0; p=0.016).
	Overall Conclusion: In twelve patients with NF1, LTG did not improve synaptic plasticity after repetitive transcranial magnetic stimulation (rTMS) in comparison to Placebo. After both (LTG and Placebo), no changes cortical excitability, a marker for synaptic plasticity was observed. In addition, we did not observe a difference in short intracortical inhibition, a marker of GABAergic inhibition that is considered the underlying mechanism of impaired synaptic plasticity in patients with NF1. No improvement of attentional performance measured by the Test of Attentional Performance (TAP) has been shown. Interestingly, we observed a significant difference in resting motor thresholds (RMT) after LTG medication. This is in conclusion with previous findings in heathy subjects and may support the hypotheses of a similar mode action of LTG in patients NF1 and healthy subjects by blocking sodium channels. In patients with Noonan syndrome, we recruited four patients of whom 2 were lost to follow up. Descriptive analyses of the two patients that completed the study revealed no obvious changes in corticospinal excitability after LTG and lovastatin (LOV) following rTMS and in SICI measurements. In the TAP analysis the Visual Scanning with and without conditioning stimulus appeared to be less after LOV medication as compared to Placebo. We observed no obvious differences after LTG medication. The Corona virus pandemic led to severe restrictions on several levels of daily life and patients visits in hospital. Mainly due to these conditions, we were unable to complete experiment I (LOV) and experiment II (LTG) in patients with Noonan syndrome. Of four patients included, two completed both experiments and two were lost to follow up. The medication with LTG in NF1 patients and LTG and LOV in NS patients was safe and well tolerated. None of the patients reported any adverse events (AEs) during the study period.

Table 1: Patient disposition (all randomized)

	Experiment																	
	NS-LOV				*NS-LTG*						*NF-LTG*							
	LOV - placebo		*Placebo - LOV*		*LTG - placebo*		*Placebo - LTG*		*Total NS*		*LTG - placebo*		*Placebo - LTG*		*Total NF*		*Study Total*	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized	0		4		1		3		4		6		6		12		16	
Included in FAS	0		2	(50%)	0		2	(67%)	2	(50%)	6	(100%)	6	(100%)	12	(100%)	14	(87.5%)
Completed first period	0		2	(50%)	0		2	(67%)	2	(50%)	6	(100%)	6	(100%)	12	(100%)	14	(87.5%)
Completed first and second period	0		2	(50%)	0		2	(67%)	2	(50%)	6	(100%)	6	(100%)	12	(100%)	14	(87.5%)
Reasons for premature discontinuation (n, %)																		
AE									0						0		0	
Withdrawal of consent									0						0		0	
Protocol deviation									0						0		0	
Lost to follow-up									2	(50%)					0		2	(12.5%)
Death									0						0		0	
Other									0						0		0	

% denote column percent with denominator “number randomized”

Table 2: Demographics and Baseline Characteristics (all randomized)

	Treatment group		
	NS (N = 4)	*NF (N = 12)*	*Total (N = 16)*
Sex (n, %)			
Female	1 (25.0%)	5 (41.7%)	6 (37.5%)
Male	3 (75.0%)	7 (58.3%)	10 (62.5%)
Age group (n, %)			
Adults (18 - 64 years)	4 (100%)	12 (100%)	16 (100%)
Age (years)			
Mean ±SD	27.8 ±5.7	36.9 ±9.2	34.6 ±9.2
Median (range)	26 (23 – 36)	38 (19 – 53)	36 (19 – 53)
Handedness (n, %)			
Right	4 (100%)	12 (100%)	16 (100%)
Left	0	0	0
Both	0	0	0
Height (cm)			
Mean ±SD	167.5 ±9.1	174.1 ±10.9	172.4 ±10.6
Median (range)	169.5 (155 – 176)	177 (155 – 189)	174 (155 – 189)
Weight (kg)			
Mean ±SD	60 ±6.8	83.1 ±14.8	77.3 ±16.7
Median (range)	62.5 (50 – 65)	88.5 (58 – 110)	78.5 (50 – 110)

Table 3: MEP amplitude by period (NF-LTG)

Sequence / *Patient number*	*MEP amplitude*											
	5 min				*30 min*				*60 min*			
	Period 1	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*
LTG / Placebo												
NF-02	1.18	0.93	0.25	2.11	1.28	1.15	0.13	2.43	0.84	1.18	-0.34	2.02
NF-03	0.54	0.37	0.17	0.91	1.37	0.22	1.15	1.59	0.43	0.52	-0.09	0.95
NF-05	0.57	0.62	-0.05	1.19	0.68	1.03	-0.35	1.71	1.58	1.00	0.58	2.58
NF-07	1.49	0.77	0.72	2.26	1.53	1.42	0.11	2.95	1.14	2.08	-0.94	3.22
NF-10	0.44	0.83	-0.39	1.27	0.62	1.35	-0.73	1.97	0.46	1.01	-0.55	1.47
NF-12	0.81	1.39	-0.58	2.20	0.74	1.36	-0.62	2.10	1.05	1.77	-0.72	2.82
Placebo / LTG												
NF-01	1.24	0.39	0.85	1.63	1.59	0.72	0.87	2.31	2.41	0.46	1.95	2.87
NF-04	0.79	0.89	-0.10	1.68	0.51	0.73	-0.22	1.24	0.64	0.49	0.15	1.13
NF-06	0.61	0.74	-0.13	1.35	0.51	0.78	-0.27	1.29	0.05	0.74	-0.69	0.79
NF-08	0.55	0.89	-0.34	1.44	0.94	0.64	0.30	1.58	0.80	0.69	0.11	1.49
NF-09	1.55	1.28	0.27	2.83	1.55	0.84	0.71	2.39	1.94	0.93	1.01	2.87
NF-11	0.91	0.59	0.32	1.50	1.18	0.74	0.44	1.92	1.45	0.92	0.53	2.37
Mean ±SD of period difference	0.08 ±0.22				0.13 ±0.30				0.08 ±0.37			
p-value (paired T-test)	0.538				0.422				0.706			

LTG / Placebo = Lamotrigin followed by placebo
Placebo / LTG = Placebo followed by lamotrigine

Table 4: MEP amplitude by treatment (NF-LTG)

Sequence / *Patient number*	*MEP amplitude*								
	5 min			*30 min*			*60 min*		
	LTG	*Placebo*	*Cross-over difference*	*LTG*	*Placebo*	*Cross-over difference*	*LTG*	*Placebo*	*Cross-over difference*
LTG / Placebo									
NF-02	1.18	0.93	0.25	1.28	1.15	0.13	0.84	1.18	-0.34
NF-03	0.54	0.37	0.17	1.37	0.22	1.15	0.43	0.52	-0.09
NF-05	0.57	0.62	-0.05	0.68	1.03	-0.35	1.58	1.00	0.58
NF-07	1.49	0.77	0.72	1.53	1.42	0.11	1.14	2.08	-0.94
NF-10	0.44	0.83	-0.39	0.62	1.35	-0.73	0.46	1.01	-0.55
NF-12	0.81	1.39	-0.58	0.74	1.36	-0.62	1.05	1.77	-0.72
Placebo / LTG									
NF-01	0.39	1.24	-0.85	0.72	1.59	-0.87	0.46	2.41	-1.95
NF-04	0.89	0.79	0.10	0.73	0.51	0.22	0.49	0.64	-0.15
NF-06	0.74	0.61	0.13	0.78	0.51	0.27	0.74	0.05	0.69
NF-08	0.89	0.55	0.34	0.64	0.94	-0.30	0.69	0.80	-0.11
NF-09	1.28	1.55	-0.27	0.84	1.55	-0.71	0.93	1.94	-1.01
NF-11	0.59	0.91	-0.32	0.74	1.18	-0.44	0.92	1.45	-0.53
Mean ±SD	0.82 ±0.35	0.88 ±0.35	-0.06 ±0.22	0.89 ±0.31	1.07 ±0.44	-0.18 ±0.30	0.81 ±0.34	1.24 ±0.71	-0.43 ±0.37
p-value(paired T-test) for treatment difference	0.640			0.420			0.075		

LTG / Placebo = Lamotrigin followed by placebo
Placebo / LTG = Placebo followed by lamotrigine

Table 5: MEP amplitude by period (NS-LOV)

Sequence / *Patient number*	*MEP amplitude*											
	5 min				*30 min*				*60 min*			
	Period 1	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*
LOV / Placebo												
--												
Placebo / LOV												
NS-01	1.49				1.01				0.81			
NS-02	0.07	0.11	-0.04	0.18	0.08	0.12	-0.04	0.20	0.07	0.10	-0.03	0.17
NS-03	1.09				1.29				1.32			
NS-04	0.95	1.64	-0.69	2.59	0.60	2.45	-1.85	3.05	0.86	1.01	-0.15	1.87

LOV / Placebo = Lovastatin followed by placebo
Placebo / LOV = Placebo followed by lovastatin

Table 6: MEP amplitude by treatment (NS-LOV)

Sequence / *Patient number*	*MEP amplitude*								
	5 min			*30 min*			*60 min*		
	LOV	*Placebo*	*Cross-over difference*	*LOV*	*Placebo*	*Cross-over difference*	*LOV*	*Placebo*	*Cross-over difference*
LOV / Placebo									
--									
Placebo / LOV									
NS-01		1.49			1.01			0.81	
NS-02	0.11	0.07	0.04	0.12	0.08	0.04	0.10	0.07	0.03
NS-03		1.09			1.29			1.32	
NS-04	1.64	0.95	0.69	2.45	0.60	1.85	1.01	0.86	0.15
Mean ±SD	0.88 ±1.08	0.90 ±0.60	0.37 ±0.46	1.29 ±1.65	0.80 ±0.58	0.95 ±1.28	0.56 ±0.64	0.77 ±0.52	0,09 ±0,08

LOV / Placebo = Lovastatin followed by placebo
Placebo / LOV = Placebo followed by lovastatin

Table 7: MEP amplitude by period (NS-LTG)

Sequence / *Patient number*	*MEP amplitude*											
	5 min				*30 min*				*60 min*			
	Period 1	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*	*Period 1*	*Period 2*	*Period difference*	*Sum*
LTG / Placebo												
--												
Placebo / LTG												
NS-02	0.06	0.06			0.05	0.09			0.06	0.07		
NS-04	1.84	1.35			1.40	0.91			2.43	2.07		

Table 8: MEP amplitude by treatment (NS-LTG)

Sequence / *Patient number*	*MEP amplitude*								
	5 min			*30 min*			*60 min*		
	LTG	*Placebo*	*Cross-over difference*	*LTG*	*Placebo*	*Cross-over difference*	*LTG*	*Placebo*	*Cross-over difference*
LTG / Placebo									
--									
Placebo / LTG									
NS-02	0.06	0.06	0.00	0.09	0.05	0.04	0.07	0.06	0.01
NS-04	1.35	1.84	-0.49	0.91	1.40	-0.49	2.07	2.43	-0.36
Mean ±SD	0.71 ±0.01	0.95 ±1.26	-0.25 ±0.35	0.50 ±0.58	0.73 ±0.95	-0.23 ±0.37	1.07 ±1.41	1.25 ±1.68	-0.18 ±0.26

LTG / Placebo = Lamotrigin followed by placebo
Placebo / LTG = Placebo followed by lamotrigine

Table 9: TMS parameters by treatment (mean ±SD)

	NF-LTG			NS-LOV		NS-LTG	
	LTG (N = 12)	*Placebo (N = 12)*	*p-value*	*LOV (N = 2)*	*Placebo (N = 4)*	*LTG (N = 2)*	*Placebo (N = 2)*
Resting motor threshold (RMT) pre	49.9 ±9.4	46.6 ±8.3	0.069	66.0 ±21.2	54.0 ±18.4	69.5 ±30.4	70.5 ±19.1
RMT post 1	52.3 ±11.1	47.7 ±10.3	**0.003**	68.0 ±29.7	56.0 ±26.3	71.5 ±31.8	75.0 ±25.5
RMT post 2	53.4 ±11.2	47.6 ±10.0	**0.001**	63.5 ±20.5	55.3 ±24.0	73.0 ±31.1	77.5 ±30.4
RMT post 3	53.0 ±11.5	47.2 ±11.7	**0.009**	63.5 ±21.9	56.3 ±29.2	68.0 ±26.9	79.0 ±25.5
Active motor threshold (AMT) pre	35.7 ±7.5	34.2 ±6.5	0.373	36.0 ±9.9	33.0 ±4.6	39.0 ±7.1	38.5 ±2.1
Intensity to target MEP of 1 mV	69.7 ±18.6	61.6 ±12.0	**0.016**	82.0 ±25.5	66.5 ±23.0	82.5 ±24.8	92.5 ±10.6
Stimulation intensity of qTBS	32.1 ±6.8	30.8 ±5.9	0.404	32.5 ±0.2	29.8 ±4.1	35.5 ±6.4	34.5 ±2.1
Stimuli count prior to intervention	153 ±38	117 ±25	0.057	97.0 ±28.3	106.3 ±37.4	153.0 ±38.2	148.5 ±9.2

Table 10: Short Interval Cortical Inhibition by treatment (mean ±SD)

	NF-LTG			NS-LOV		NS-LTG	
	LTG (N = 12)	*Placebo (N = 12)*	*p-value*	*LOV (N = 2)*	*Placebo (N = 4)*	*LTG (N = 2)*	*Placebo (N = 2)*
SICI unkond. Stimimulus 1 in mV	0.68 ±0.54	0.57 ±0.45	0.250	0.62 ±0.71	0.78 ±0.48	0.87 ±1.22	0.38 ±0.40
SICI unkond. Stimimulus 2 in mV	0.28 ±0.26	0.24 ±0.25	0.572	0.17 ±0.15	0.25 ±0.18	0.38 ±0.52	0.10 ±0.04
SICI unkond. Stimimulus 3 in mV	0.46 ±0.37	0.40 ±0.36	0.551	0.68 ±0.53	0.36 ±0.15	0.38 ±0.52	0.37 ±0.01
SICI unkond. Stimimulus 4 in mV	0.54 ±0.47	0.47 ±0.38	0.527	0.62 ±0.59	0.73 ±0.45	0.58 ±0.81	0.64 ±0.09
SICI raio 2 ms	0.43 ±0.31	0.63 ±0.54	0.194	0.36 ±0.16	0.44 ±0.28	0.71 ±0.40	0.43 ±0.32
SICI raio 3 ms	0.64 ±0.40	0.72 ±0.34	0.516	1.73 ±1.12	1.37 ±1.98	0.74 ±0.43	2.12 ±2.23
SICI raio 5 ms	0.78 ±0.48	1.00 ±0.71	0.379	1.29 ±0.52	1.79 ±1.84	0.87 ±0.28	3.38 ±3.56

Table 11: TAP testing by treatment (mean ±SD)

	NF-LTG			NS-LOV		NS-LTG	
	LTG (N = 12)	*Placebo (N = 12)*	*p-value*	*LOV (N = 2)*	*Placebo (N = 4)*	*LTG (N = 2)*	*Placebo (N = 2)*
Alertness negativ WT	236.5 ±19.5	242.8 ±31.4	0.433	237.0 ±2.8	240.3 ±19.6	259.0 ±25.5	243.0 ±4.2
Alertness positiv WT	237.8 ±28.0	245.2 ±36.7	0.273	234.0 ±7.1	244.5 ±29.7	250.5 ±14.9	238.0 ±15.6
Visual Scanning CS	2717 ±633	3026 ±674	0.111	2796 ±173	3465 ±778	2340 ±282	2591 ±480
Visual Scanning nCS	4937 ±1155	5644 ±1429	0.087	4501 ±300	5240 ±1257	4451 ±300	4368 ±1083
GoNo Go task	352.8 ±44.9	380.3 ±70.8	0.116	423.5 ±30.4	391.3 ±33.4	421.5 ±0.7	416.0 ±39.6
Incompatibility CC	412.5 ±59.1	439 ±81.3	0.125	374.5 ±3.5	398.5 ±45.9	387.5 ±2.1	406.0 ±28.3
Incompatibility nCC	473.6 ±73.6	501.7 ±108.1	0.199	431.5 ±12.0	413.0 ±42.1	410.5 ±12.0	433.5 ±6.4