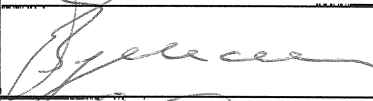
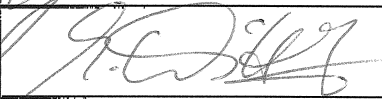
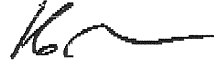


Clinical Study Report (Synopsis ICH E3)

Study Title:	Differential effect of Carbamazepine on cortical excitability in subjects with different genotypes for SCN1A as measured by transcranial magnetic stimulation (TMS)	
Study Acronym	EPICURE SP 5- TMS- SCN1A	
Study Sponsor-ID	KKS-115	
EudraCT No.	2008-003392-40	
CSR Version	V01F	
CSR Date	2012-07-03	
	Date	Signature
Author Dr. Eckhard Bergmann	2012-07-05	
Review <i>Dr. M. Wittenberg</i> Sylvia Reinecker	2012-07-05	
Sponsor Prof. Dr. Felix Rosenow	2012-07-03	

Index

1	Name of Sponsor/Company	3
2	Name of Finished Product.....	3
3	Name of Active Substance	3
4	Individual Study Table: Referring to Part of the Dossier (Volume, Page)	3
5	Title of Study	3
6	Investigators.....	3
7	Study centre(s)	3
8	Publication (reference)	3
9	Studied period (years): date of first enrolment, date of last completed	3
10	Phase of development	3
11	Objectives	4
12	Methodology.....	4
13	Number of patients (planned and analysed)	4
14	Diagnosis and main criteria for inclusion.....	4
15	Test product, dose and mode of administration, batch number	4
16	Duration of treatment.....	4
17	Reference therapy, dose and mode of administration, batch number	4
18	Criteria for evaluation: Efficacy, Safety	4
19	Statistical methods	4
20	Summary - Conclusions: Efficacy Results, Safety Results, Conclusion.....	4
21	Date of report	5

Clinical Study Report (Synopsis ICH E3)

1 Name of Sponsor/Company

Philipps-Universität Marburg, Biegenstrasse 10, 35037 Marburg

2 Name of Finished Product

Tegretal 200mg

3 Name of Active Substance

Carbamazepine

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N.A.

5 Title of Study

„Untersuchung des Einflusses von Carbamazepin auf die mittels transkranieller Magnetstimulation gemessene kortikale Exzitabilität des menschlichen Motorkortex in Abhängigkeit vom Polymorphismus für SCN1A“ (**Version V03F vom 27.02.2009**)

Datum der BfArM Genehmigung (BfArM Vorlagen Nummer)	26.03.2009 4034948
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V	
N.A.	
Datum der zustimmenden Ethik Bewertung (Aktenzeichen der EK Uni Marburg)	06.04.2009 EK MR: 02/09 (A)
Ggf. Daten von Genehmigungen nachträglicher Änderungen nach § 10 Abs. 1 GCP-V	
N.A.	

6 Investigators

F. Rosenow, K. Menzler, P.S. Reif, K.M. Klein, A. Haag, A. Hermsen, I. Immisch, S. Wegner, C. Roth, C. Pohl, H. Bugiel, C. Duddek, K. Balkenhol, K. Hallenberger

7 Study centre(s)

Neurologische Klinik mit Poliklinik
Philipps-Universität Marburg
und UKGM GmbH, Standort Marburg
vormals: Rudolf-Bultmann-Str.8
vormals: 35033 Marburg

8 Publication (reference)

The influence of Carbamazepine on Cortical Excitability depends on SCN1A Polymorphism Genotype – A Pharmacogenetic TMS-Study (in prep.), Menzler K., Hermsen A. et al.

9 Studied period (years): date of first enrolment, date of last completed

Date of first enrolment: 2009-09-16

Date of last completed: 2011-06-24

10 Phase of development

N.A.

11 Objectives

To investigate the effects of the SNP genotype on cortical excitability at baseline and after administration of carbamazepine

12 Methodology

Transcranial magnetic stimulation (TMS)

13 Number of patients (planned and analysed)

Planned: screening 250, analysis 56 AA & 50 GG

Analyzed: screening 304, analysis 92 volunteers (49 with genotype AA and 43 with genotype GG).

14 Diagnosis and main criteria for inclusion

Either *SCN1A* IVS5N+5 G>A polymorphism, homzygote variants AA or GG. Main inclusion criteria were right-handedness as determined by the Edinburgh Handedness Inventory (EHI, EHI-score \geq 80), age 18-60 yrs, „safe“ contraception for women (Pearl index <0.1) and the cognitive and physical ability to understand the experimental procedure, take the antiepileptic medication and be investigated by TMS.

15 Test product, dose and mode of administration

Carbamazepine 400mg, oral application

16 Duration of treatment

There were 2 TMS measurements with a time lag of at least 2 weeks, i.e. the treatment duration per patient was at least 2 weeks.

17 Reference therapy, dose and mode of administration, batch number

Placebo (P-Tabletten Lichtenstein), oral application

18 Criteria for evaluation: Efficacy, Safety

Efficacy Criteria: resting motor threshold (RMT), short interval intracortical Inhibition (sICI), intracortical facilitation (ICF), Silent Period (SP)

Safety Criteria: Assessment of AEs and SAEs

19 Statistical methods

Statistical analysis was computed with IBM® SPSS® Statistics 20 (SPSS, IBM Company, Chicago, Illinois). Chi-Square-tests were applied to categorical variables and t-tests for independent samples to metric variables, respectively.

For overall effects of treatment and comparing CBZ vs. Placebo irrespective of genotype t-tests for paired samples were used.

20 Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

Safety results: In the course of the study period there were two SAEs (Appendectomy and Meniscus surgery), which both occurred prior study treatment. Therefore they were not related to the study medication.

Efficacy results and conclusion:

We showed a differential effect of carbamazepine on the CSP duration which depended on the *SCN1A* SNP genotype and reflects changes in GABA-ergic cortical inhibition.

21 Date of report

2012-07-03