Aus der Klinik für kleine Haustiere
und dem Institut für Pharmakologie, Toxikologie und Pharmazie
der Tierärztlichen Hochschule Hannover

Klinische Pilotstudie zur Prüfung einer neuen antiepileptischen Wirksubstanz an Hunden mit idiopathischer Epilepsie

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Abbreviations

Abb.	Abbildung
ALT	alanine transferase, Alanin – Amino - Transferase
AP	alkaline phosphatase, Alkalische Phosphatase
µg	microgram, Mikrogramm
µL	microliter, Mikroliter
AWD 131-138	[1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one]
bld	below limit of detection
bzw.	beziehungsweise
ca.	circa
CNS	Central Nervous System
CT	computed tomography, Computertomographie
Diff.	differential cell - count, Differentialblutbild
EDTA	ethylene diamine tetraacetate Ethylendiamintetraacetat
EEG	elektroencephalogram, Elektroenzephalogramm
Fig.	figure
f	female
GABA	γ - amino - butyric acid, Gamma - Aminobuttersäure
$GABA_A$	subtypes of GABA – receptors,
GLDH	glutamate dehydrogenase, Glutamat – Dehydrogenase
h	hour

HPLC	high performance liquid chromatography, Hochleistungsflüssigkeitschromatografie
HWZ	half-life time, Halbwertszeit
KBr	potassium bromide, Kaliumbromid
kg	kilogram, Kilogramm
MRI	Magnetic resonance imaging Kernspintomographie
m	male
mg	milligram, Milligramm
min.	minute, Minute
mL	milliliter, Milliliter
n	number
nf	neutered female
ng	nanogram, Nanogramm
nm	neutered male
P	significant range, Signifikanzbereich
p.o.	per oral
resp.	respectively
SEM	Standard error of the mean, Standardfehler des Mittelwerts
Tab.	Table, Tabelle
u.a.	und andere
z.B.	zum Beispiel
ZNS	Zentrales Nervensystem

special signs:

%	percent, Prozent
®	eingetragenes Warenzeichen
™	trade mark

I Introduction

Epilepsy is a common disease in dogs. The frequently occurring cause of recurrent seizures in dogs is idiopathic epilepsy (SCHWARTZ-PORSCHE 1994, BERNARDINI and JAGGY 1998). The intervention for this disease is a life-long treatment with antiepileptic drugs mostly deriving from human medicine. It is emphasized that only a few of the current anticonvulsant drugs are suitable for chronic treatment in dogs, which includes phenobarbital, primidone and potassium bromide.

The effects of these drugs were studied in clinical trials in epileptic dogs (GALLAGHER and FREER 1985, SCHWARTZ-PORSCHE et al. 1985, FREY and SCHWARTZ-PORSCHE 1985, BUNCH 1986, HONHOLD and MORTON 1988, FORRESTER et al. 1989, FREY 1989, FENNER and HAAS 1989, SCHWARTZ-PORSCHE and JÜRGENS 1991, LÖSCHER 1994). However, carefully monitored treatment will lead only to a significant reduction of seizure frequency in two third of the cases, whereas one third of the dogs will be pharmacoresistent to the traditional therapy (SCHWARTZ-PORSCHE et al. 1982, LÖSCHER et al. 1985, LÖSCHER and SCHWARTZ-PORSCHE 1986, FREY 1989, PODELL and FENNER 1993 and HEYNOLD et al. 1997). During this conventional treatment many side effects can be observed such as sedation, ataxia, polyphagia, polydipsia, polyuria and an elevation of liver enzymes (LÖSCHER et al. 1985). Newer antiepileptic drugs are not recommended because of an insufficient half-life in dogs (LÖSCHER 1994). However, for therapyresistent dogs the need of newer and better tolerated antiepileptic drugs is obvious.

In preclinical studies a novel antiepileptic drug, AWD 131-138 showed a potent anticonvulsive effect in dogs and an adequate half-life time (LÖSCHER and POTSCHKA 1998a, unpublished data). Based on these facts this clinical pilot study was designed to verify the anticonvulsive

efficacy of the new substance AWD 131-138 in dogs with newly diagnosed and chronic idiopathic epilepsy in comparison to conventional antiepileptic drugs. Seizure frequency, duration and severity as well as possible occurring side effects should be evaluated.

II Literature review

II.1 Epilepsy in history

Epilepsy was documented for the first time 2080 before Christ in the laws of Babylon of Hammurabis. Hippokrates (460-357 before Christ) described epilepsy as a "sacred disease" and people with epilepsy were under a demonic or other spiritual possession (TEMKIN 1945, SCOTT 1969, CUNNINGHAM 1971). Hippokrates estimated epilepsy as a disease of natural causes and the brain of being the primary region affected. His opinion was accepted from physicians and medical schools during the next centuries.

In the Middle Ages epilepsy was not further investigated. People rather believed that people with seizures are being visited by god. In the 17th and 18th century epilepsy was considered again as being a pathological condition.

Many centuries passed with countless people undergoing barbaric treatment and social isolation. First clinical observations in epileptic people were studied in French hospitals during the early 19th century. In this period seizures were observed also in animals by CHAVEAU (1865) (JOEST 1902). JOEST (1902) described that infectious diseases such as canine distemper encephalitis may initiate seizures. Epilepsy was found in horses, cattle, and pigs, however, dogs were the most frequently affected species. At this time point, it was mentioned, that young dogs without a predisposition of gender were more frequently affected.

In the second part of the 19th century the 2000 year old statement was scientifically proven by FRITSCH and HITZIG (1870). These authors could show that the brain is the starting point of epilepsy and found that electric stimulation of the cerebrum causes seizures in dogs (IPPISCH 1987). In

further experiments with dogs FERRIER (1843-1928) could prove that focal seizures correlate with a local brain lesion whereas generalized seizures involve to the whole cortex (JANZ 1969, IPPISCH 1987).

II.2 Definition

Different synonyms for epilepsy are used, but characterize sudden, excessive transient paroxysmal neuronal discharges in the cerebral cortex (LÖSCHER 1993, JAGGY and STEFFEN 1995a). Spreading of this activity to different parts of the brain (LÖSCHER 1993, JAGGY and STEFFEN 1995a) leads to different clinical manifestations such as behavioral changes, altered motoric, sensoric and/or autonomic functions and abnormal mental status OLIVER (1980) (figure 1).

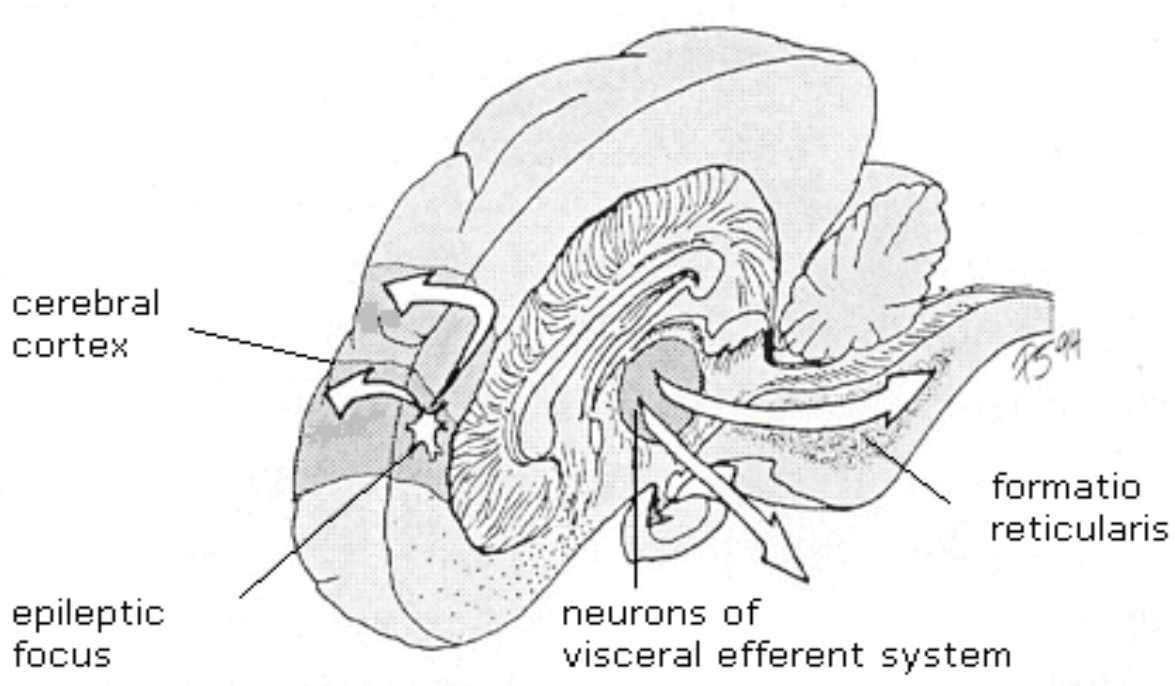


Figure 1: Longitudinal section of the right cortex

The activity of the epileptic focus, localized in the motor cortex spreads to other parts of the cerebral cortex, to the other hemisphere, to neurons of

the visceral efferent system, the brainstem and the formatio reticularis (modified after JAGGY and STEFFEN 1995a).

II.3 Epidemiology

Seizure disorders are the most common intracranial neurologic diseases in human beings and animals, particularly dogs and cats (OLIVER 1980, SCHWARTZ-PORSCHE 1984, LÖSCHER et al. 1985, FREY 1989). Among domesticated animals, epilepsy seems to be fairly common in dogs (CROFT 1965, CUNNINGHAM 1971). In the dog as well as in man, seizure disorders have an estimated morbidity of 0,5-1% (US Department of Health, Education and Welfare 1977, JANZ 1979, LÖSCHER et al.1985, KERÄNEN and RIEKKINGEN 1988, FORRESTER et al. 1989, SRENK et al. 1994).

II.4 Epileptology

Considerable progress understanding underlying mechanisms has been made.
An imbalance between inhibitory (BURNHAM 1989, LÖSCHER 1989) and excitatory neurotransmitters (MCNAMARA 1988, DINGLEDINE et al. 1990) has been described (FENNER and HAAS 1989). Also altered ion channels and neurotransmitter receptor functions seem to play a significant role in the pathogenesis of epilepsy (OWENS and KRIEGSTEIN 2001).

The underlying mechanism of epileptic seizures is an increased excitability of nerve cells which might be inherited or acquired (OLIVER 1987, RUTISHAUSER and KRAYENBÜHL 1987, CHRISMAN 1991, OLIVER and LORENZ 1993, JAGGY and STEFFEN 1995a). Dogs with hereditary epilepsy (JAGGY and STEFFEN 1995a) have a low epileptic threshold. Although

many scientists perform research about etiology and epileptogenesis the knowledge on epilepsy is still not completely understood.

II.5 Classification

In human, seizures were classified by the COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY (1989) into either partial or generalized seizures, unclassified seizures and status epilepticus based on clinical signs and electroencephalographic findings. Further epilepsy is defined as either idiopathic or symptomatic.

In dogs seizures are classified as either partial or generalized seizures with tonic, clonic or tonic-clonic activity, with or without loss of consciousness (SCHWARTZ-PORSCHE 1984, PODELL et al. 1995). Epilepsy is defined as idiopathic, when no underlying causes can be defined by clinical and pathological examinations (CUNNINGHAM 1971, DE LAHUNTA 1983, MONTGOMERY and LEE 1983, SCHWARTZ-PORSCHE 1984, CHRISMAN 1991, JAGGY and STEFFEN 1995 b and c). Symptomatic epilepsy is caused either by an intracranial lesion or an extraneural, metabolic disturbance (JAGGY and STEFFEN 1995 b and c, PODELL et al. 1995, JAGGY and HEYNOLD 1996).

II.6 Seizure types

Simple partial seizures are clinically asymmetric signs without a change in consciousness and should be suspicious of a focal intracranial lesion. Examples includes facial focal seizures, excessive pawing or biting of a body part or tonic-clonic convulsions in one limb.

Dogs with complex partial seizures have impaired consciousness often with bizarre behavioral activity, possibly combined with secondary generalization. A special kind of complex focal seizures are psychomotoric seizures. These dogs may show "fly-biting imaginary insects", funny behavior patterns, become aggressive without provocation, howl incessantly, become restless, or are tail chasing (COLTER 1989).
In veterinary medicine primary generalized convulsions are seen as the most common seizure type (OLIVER 1980). These seizures are characterized by impaired consciousness and tonic, clonic or tonic-clonic activity, in most cases combined with spontaneous urination and defecation (SCHWARTZ-PORSCHE 1984, PODELL et al. 1995, JAGGY and STEFFEN 1995a). Typical sequences of generalized seizures (grand mal type) in a dog are shown in figure 2.

Generalized epileptic seizures can be isolated (one per 24 hours), clustered (2 or more per 24 hours) or continuous (30 minutes or longer) without recovery and return to normal consciousness (status epilepticus) (PODELL 1996).

II.7 Symptoms of generalized epileptic seizures

The clinical features of classical generalized epileptic seizures (grand mal) are divided into the following components (see figure 2).
Some pet-owners reported that they know when their dogs are going to seizure days in advance by changes in the dogs behavior. These prodromal signs continue from seconds to hours and are characterized mainly by restlessness, anxiety, salivation, tremor, uncontrolled barking and sometimes by vomitus (JAGGY and STEFFEN 1995a, HEYNOLD et al. 1997).

The initial manifestation of an epileptic seizure is the aura. During this period, which is generally of short duration, dogs can exhibit stereotypic sensoric or unilateral focal motor activity of the head and the limbs (pacing, licking) or signs of an altered autonomic nervous system (salivating, urinating, vomiting), or can show unusual behavior (excessive barking, increased devotion) (JAGGY and STEFFEN 1995a, PODELL 1996 and HEYNOLD et al. 1997).

The ictus is the actual seizure event lasting from seconds to several minutes and is characterized by increased muscle tone and/or involuntary excessive movements and/or abnormal sensations or behavior with loss of consciousness (figure 2). Automatisms in the limbs can be observed. Most dogs are salivating, urinating or defecating during this period.

After the ictus in most of the dogs a postictal phase is observed with unusual behavior, compulsive walking, restlessness, disorientation, abnormal bowel/bladder activity, polydipsia or polyphagia and/or actual neurologic deficits such as weakness, central blindness, or sensory and motor dysfunctions. The postictal period lasts from some minutes to several days (JAGGY and STEFFEN 1995a, PODELL 1996, HEYNHOLD et al. 1997).

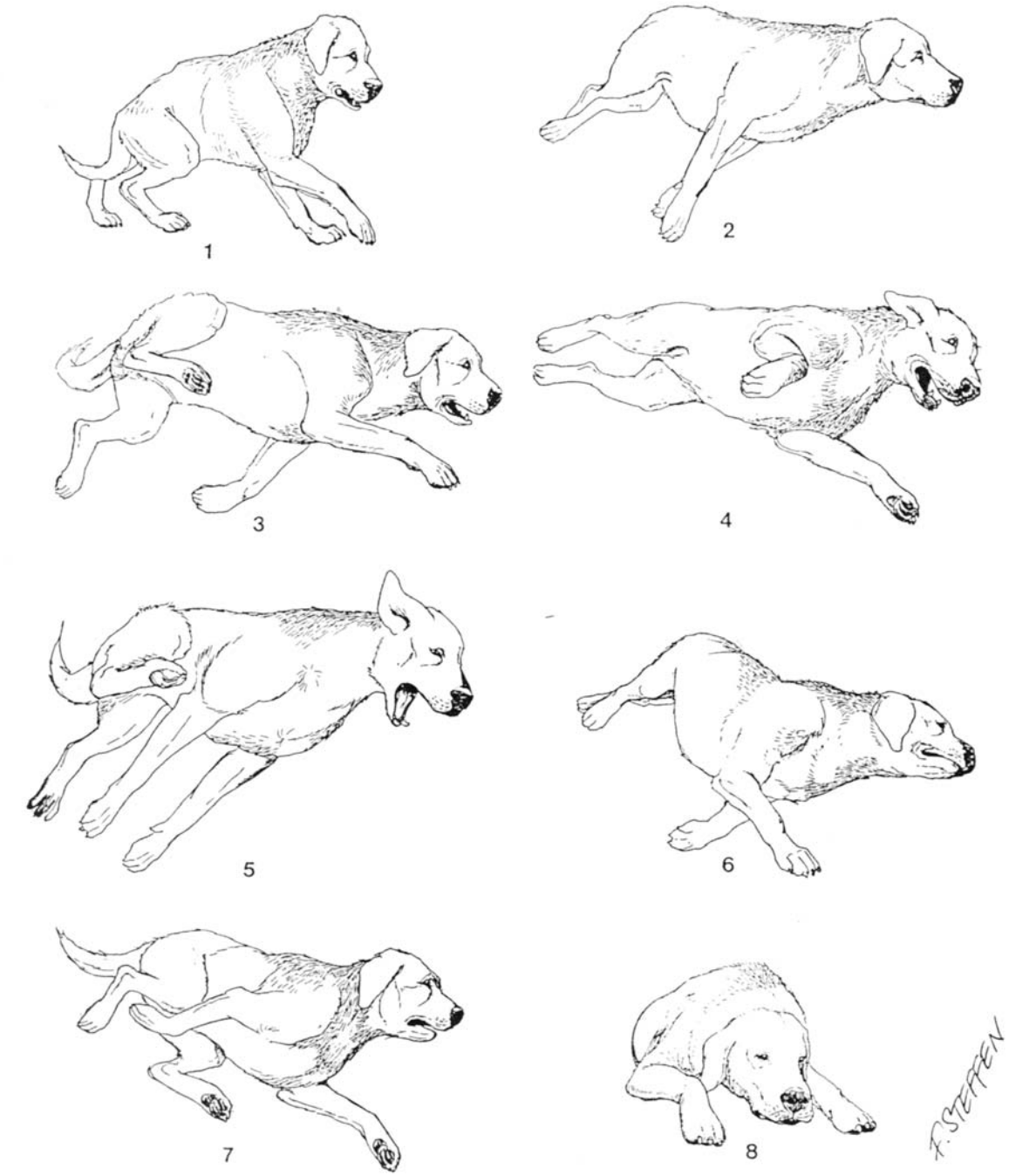


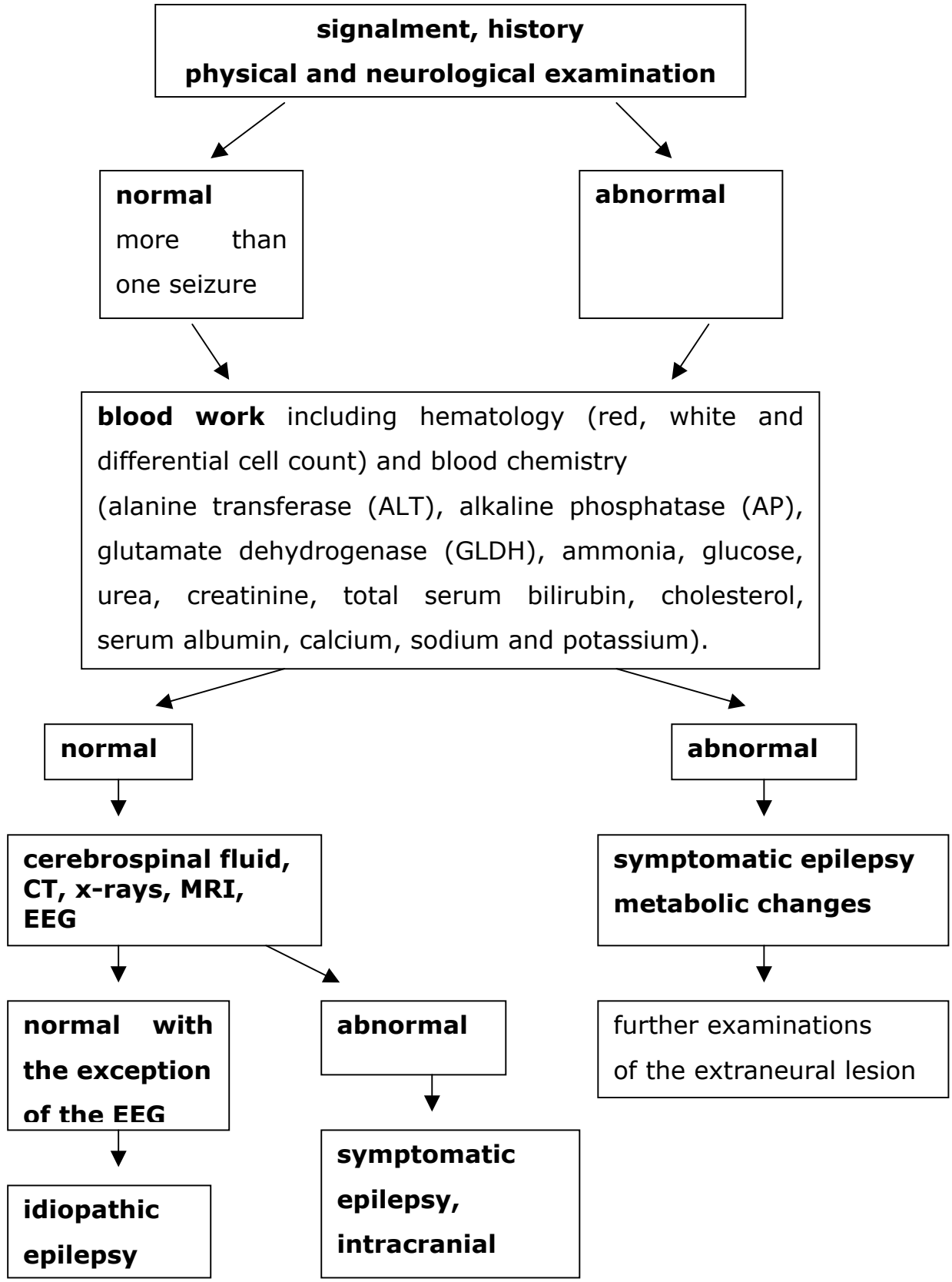
Figure 2: Sequences of grand mal seizures in a Labrador Retriever modified after HEYNOLD et al (1997)

1. aura, **2.-7.** ictus, **2.** increased muscle tonus of the forelimbs, **3.** paddling of all limbs (automatisms), **4. + 6.** paddling of the forelimbs, **5.** excessively increased muscle tonus of the forelimbs, **7.** tonic-clonic seizure activity, **8.** postictal phase

II.8 Clinical diagnosis

For the clinical diagnosis and treatment suggestions careful diagnostic work-up is necessary. The diagnosis "idiopathic epilepsy" can only be supported by excluding different diseases leading to seizure activity. Mostly the diagnostic procedure is performed step by step (see the following flow chart 1). It includes the history, especially about the clinical features of the seizures, signalment, clinical and neurological examination. Ancillary investigations are necessary to exclude metabolic disturbances or intracranial diseases. Blood work is performed, evaluating red, white and differential cell count and blood chemistry (alanine transferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), ammonia, glucose, urea, creatinine, total serum bilirubin, cholesterol, serum albumin, calcium, sodium and potassium). Further examinations include urinanalysis, analysis of the cerebrospinal fluid, electroencephalography, several imaging techniques such as radiographs of the thorax, or the abdomen, ultrasonography of the abdomen and computed tomography or magnetic resonance imaging of the skull.

Flow chart 1: Scheme for the diagnostic work-up in dogs with seizures:



II.9 Differential diagnosis

Seizures may be caused by extraneural, intracranial or idiopathic diseases, which lead to metabolic and/or functional changes in the brain (JAGGY and STEFFEN 1995 a, b and c).
Several extraneural diseases may be the cause for seizures by changing the metabolism of the brain. These diseases include metabolic disturbances such as hypoglycemia, hypoxia, hypocalcaemia, hypothermia, policytemia, uremic and hepatic encephalopathy, various intoxications and hypothyroidism. The diagnosis of these extraneural diseases is supported in most cases by results of blood work and urinalysis. Approximately 10 percent of seizure disorders are caused by these extraneural diseases (JAGGY and STEFFEN 1995 b).

Intracranial diseases as causes for seizures include hemorrhage, inflammatory-infectious diseases, trauma, anomalies, tumors, infarcts, metabolic and degenerative changes (JAGGY and STEFFEN 1995 c). These different diseases acquire additional diagnostic workup and other treatment approaches as performed in cases with idiopathic epilepsy.

II.10 Idiopathic epilepsy

The diagnosis of idiopathic epilepsy is based on normal physical, neurological and special examinations (see flow chart 1). In dogs, idiopathic epilepsy is diagnosed in approximately 45% of cases with seizure disorders (JAGGY and STEFFEN, 1995 a and c), and in 5,3 - 8,0% of all dogs with diseases of the nervous system (SCHWARTZ-PORSCHE 1994, BERNARDINI and JAGGY 1998). In most of the canine cases with idiopathic epilepsy generalized seizures (80-90%) are observed (SCHWARTZ-PORSCHE 1984, LÖSCHER et al. 1985, BRAUND 1986,

CENTER 1986, JAGGY and STEFFEN, 1995 c). However, partial seizures may occur (BREITSCHWERDT et al. 1979).

Seizure activity commonly starts in dogs with idiopathic epilepsy at an age of 1-3 years (CROFT 1965, CUNNINGHAM 1971, DE LAHUNTA 1983, FORRESTER et al. 1989, OLIVER and LORENZ, 1993, VANDEVELDE et al. 2001). In some breeds inheritance was proven (OLIVER 1987, CHRISMAN 1991, OLIVER and LORENZ 1993, JAGGY and STEFFEN 1995a, SRENK et al. 1994, JAGGY et al. 1998), a certain predisposition for idiopathic epilepsy was shown for some dog families (VAN DER VELDEN 1968, MARTINEK and HORAK 1970, BIELFELT et al. 1971, BRASS and HORZINEK 1971, WALLACE 1973, FALCO et al. 1974, URBRICH 1974, CUNNINGHAM and FARNBACH 1988). Principally all breeds can be affected.

II.11 Antiepileptic drugs

Chronic administration of antiepileptic drugs is the treatment of first choice in epilepsy. The selection of an antiepileptic drug is based primarily on its efficacy for specific types of seizures and epilepsy (LÖSCHER 1997). Due to the strong clinical similarity between human and canine epilepsy the epileptic dog represents also an ideal tool to study the efficacy of antiepileptic drugs in man (LÖSCHER, 1984).

However, in dogs only a few antiepileptic drugs can be used successfully as a life long treatment, such as phenobarbital, primidone and potassium bromide (SCHWARTZ-PORSCHE 1984, FREY and SCHWARTZ-PORSCHE 1985, SCHWARTZ-PORSCHE et al. 1985, FREY 1986, SCHWARTZ-PORSCHE and JÜRGENS 1991, LÖSCHER 1994). Monotherapy is the initial goal of treating dogs with epilepsy to reduce possible drug interactions and adverse effects. Treatment outcome after applying these three drugs

is not in all cases satisfactory. In about one third of the cases, pharmacoresistency is observed (SCHWARTZ-PORSCHE et al. 1982, FREY and SCHWARTZ-PORSCHE 1985, LÖSCHER et al. 1985, LÖSCHER and SCHWARTZ-PORSCHE 1986, HEYNOLD et al. 1997). Furthermore, using phenobarbital respectively primidone side effects may occur such as excessive sedation, ataxia, compulsive pacing, weakness, polyphagia, polydipsia and polyuria (SCHWARTZ-PORSCHE et al. 1982 and LÖSCHER 1995). An elevation of liver enzymes is frequently observed (LÖSCHER 1995). Treatment with potassium bromide can result in tiredness, anorexia, obstipation, gastritis and skin lesions (LÖSCHER 1995). Potassium bromide (KBr) is either used as a monotherapy or as add-on medication to phenobarbital to reduce refractory epilepsy (PEARCE 1990, SCHWARTZ-PORSCHE and JÜRGENS 1991, PODELL and FENNER 1993 and 1994). Dogs developing tolerance to phenobarbital or primidone during chronic administration are treated with potassium bromide as second antiepileptic drug. Focal seizures have been successfully managed with felbamate in six dogs (RUEHLMANN et al. 2001).

Newer antiepileptic drugs such as gabapentin or lamotrigine are not recommended because of an insufficient half-life (LÖSCHER 1994). This difference in pharmacokinetic behavior complicates the use of epileptic dogs as an ideal model of human epilepsy and only drugs with sufficient long half-lives in dogs can be tested. However, the need for new antiepileptic drugs for dogs is obvious.

II.12 AWD 131-138

AWD 131-138, [1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one] is a new drug with anticonvulsant and anxiolytic effects (ROSTOCK et al., 1998a-d). The mechanism of action of AWD 131-138 is not fully understood until now. A very low affinity for the benzodiazepine binding site of the $GABA_A$ receptor was found in a broad receptor screen. Electrophysiological studies using different cloned human GABA receptor complexes indicate that AWD 131-138 acts as a low affinity partial agonist at the benzodiazepine receptor without subtype selectivity. The maximal stimulation obtained with AWD 131-138 reached only 20% of the effect of diazepam. The specific receptor antagonist flumazenil was used to assess the contribution of the benzodiazepine receptor interaction for the pharmacological activity. The anticonvulsive activity of AWD 131-138 could be partly antagonized, and the anxiolytic activity was fully antagonized upon co-administration of flumazenil. The extent of the antagonism in the seizure and anxiety test was comparable with the effect of flumazenil on the anticonvulsive and anxiolytic activity of diazepam. These data indicate that, despite the low affinity and the low intrinsic activity, the interaction of AWD 131-138 with the benzodiazepine receptor may be the main mechanism of the pharmacological activity. However, the psychopharmacological profile of AWD 131-138 differs considerably from known benzodiazepine agonists. In a drug discrimination study, monkeys did not identify AWD 131-138 as benzodiazepine-like, as they did with midazolam and diazepam. This lack of benzodiazepine like psychopharmacology was also substantiated in a self administration paradigm where AWD 131-138, unlike full benzodiazepine agonists, did not substitute for cocaine. This lack of benzodiazepine like psychopharmacology may be related to the partial agonistic activity with low intrinsic activity. AWD 131-138 was also found to have weak calcium channel blocking effect. This mechanism may contribute to the

anticonvulsant activity (ROSTOCK et al. 1998a-d, RUNDFELDT et al. 1998, SIGEL et al. 1998, YASAR et al. 1999).
Pharmacokinetic experiments and investigations of tolerance and dependence development during chronic administration showed a potent anticonvulsant effect in dogs (LÖSCHER and POTSCHKA unpublished data, 1998b). During these trials no evidence of an accumulation in plasma concentrations or an induction of a metabolic tolerance was found (LÖSCHER and POTSCHKA, unpublished data 1998b). LÖSCHER and POTSCHKA (unpublished data, 1998a) could show that dogs tolerated AWD 131-138 well during chronic administration and this new drug allows an effective chronic treatment in dogs because of its long half-life after oral administration. These authors could demonstrate anticonvulsant activity of AWD 131-138 in the pentylentetrazol-threshold test resulting in acute generalized seizures in dogs (LÖSCHER and POTSCHKA unpublished data, 1998a).

The purpose of the present study was to evaluate the efficacy of this new anticonvulsant substance AWD 131-138 in a clinical pilot trial in dogs with idiopathic epilepsy. Dogs with newly diagnosed idiopathic epilepsy without any pretreatment and dogs with idiopathic epilepsy which did not respond to conventional antiepileptic medication were treated with this new substance. For comparison a retrospective study on the treatment outcome with similar groups of dogs and conventional medication was performed.

III Materials and methods

III.1 Dogs

In the present study 111 dogs with idiopathic epilepsy were examined. In a prospective study 29 dogs were treated with AWD 131-138. In 12 dogs with newly diagnosed idiopathic epilepsy (newly diagnosed dogs) the initial anticonvulsant treatment was started with AWD 131-138. In further 17 dogs with chronic epilepsy and no response to conventional treatment AWD 131-138 was added (add-on treatment). Retrospectively, we evaluated 82 dogs with idiopathic epilepsy. 70 newly diagnosed dogs were treated with the established antiepileptic drugs phenobarbital or primidone. In the remaining 12 dogs with chronic epilepsy, without any improvement after treatment with these two drugs, potassium bromide was supplemented (table 1).

Table 1: Number of dogs included in the present study

treatment	**number of dogs**
1. AWD 131-138	**29**
- dogs with idiopathic epilepsy, newly diagnosed	12
- dogs with chronic idiopathic epilepsy phenobarbital or primidone add-on AWD 131-138	17
2. conventional therapy	**82**
- dogs with idiopathic epilepsy, newly diagnosed phenobarbital monotherapy	44
- dogs with idiopathic epilepsy, newly diagnosed primidone monotherapy	26
- dogs with chronic idiopathic epilepsy phenobarbital or primidone add-on potassium bromide	12

III.1.1 Dogs: AWD 131-138 treatment

The first part of this investigation represents a clinical pilot study testing a new anticonvulsant substance AWD 131-138 [1-(4-Chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one]. At the beginning of the AWD 131-138 treatment all owners had to agree that the dog will be included in the study and sign a form (see appendix, form 3). 29 dogs with a history of seizure disorders were diagnosed with idiopathic epilepsy from October 2000 to February 2001 at the Department for Small Animal Medicine and Surgery, School of Veterinary Medicine Hannover.

III.1.1.1 Newly diagnosed dogs

In twelve of these dogs idiopathic epilepsy was newly diagnosed. They were not treated prior to presentation and received a monotherapy with AWD 131-138 (table 1). One of these dogs showed after 4 months of AWD 131-138 treatment no improvement of the seizure frequency and phenobarbital (4 mg/kg bodyweight p.o., daily dosage) was supplemented.

Seven different breeds (75%) and three mixed breed dogs (25%) entered this part of the study. Breeds included: German Shepherd (n=3), Golden Retriever, American and English Cocker Spaniel, Newfoundland, Irish Setter, German Shorthair Pointer (each: n=1) (table 16, appendix). The dogs ranged in age from 2 ½ to 13 years, (median age 4.5 years, mean and standard deviation 4.6 ± 1.2 years). The pet owners observed first occurrence of seizures between an age of 1 ½ years to 12 ¾ years (median age 2.0 years, mean and standard deviation 2.4 ± 1.0 years). Of all 12 dogs, 8 (67%) were intact males, 3 (25%) intact females and 1 (8%) was a spayed female.

All dogs had prior to the presentation two or more generalized epileptic seizures. Grand mal seizures were observed by the owners in all cases,

5 of them developed cluster of seizures. In addition to generalized seizures in 3 dogs focal seizures were noticed (table 2). Seizure frequency in the 12 untreated dogs ranged from eight seizures per month to one seizure every eight months (table 11, appendix).

III.1.1.2 Dogs with chronic epilepsy

Seventeen dogs with chronic epilepsy had been treated with phenobarbital or primidone before presentation and did not respond to this conventional medication. The treatment period ranged from 3 months to 5 years (median 1.5 years, mean and standard deviation 1.6 ± 1.3 years). These animals received during the pilot study a combination therapy of either phenobarbital or primidone combined with AWD 131-138 (table 1).
Eleven of these dogs were treated with daily dosages of phenobarbital from 6 to 23 mg/kg bodyweight p.o. (median 10.7, mean and standard deviation 12.9 ± 6.6 mg/kg). Serum concentrations of phenobarbital were measured and ranged from 19.5 to 58.9 µg/mL (median 26.5, mean and standard deviation 32.0 ± 13.6 µg/mL; reference values 15 – 45 µg/mL, established by FARNBACH 1984).
The remaining six dogs were treated with primidone using daily dosages from 25 to 53 mg/kg bodyweight p.o. (median 45.5, mean and standard deviation 42.8 ± 8.9 mg/kg). In these cases phenobarbital concentration ranged from 23.2 to 27.4 µg/mL (median 23.7, mean and standard deviation 24.8 ± 1.8 µg/mL).
Twelve different breeds (76%) and four mixed breed dogs (24%) entered the study. Breeds included: German Shepherd (n=2), Golden Retriever, Boxer, Jack Russell and West Highland White Terrier, Magyar Viszla, Miniature Poodle, English Springer Spaniel, Rottweiler, German Wirehair Pointer, Fox Terrier and Collie (each: n=1) (table 19, appendix). The dogs ranged in age from 1 ¼ to 9 ½ years, (median age of 4.5 years, mean and standard deviation 4.7 ± 1.9 years). The pet owners observed first

occurrence of seizures between an age of 6 months to 8 ½ years (median age of 2.2 years, mean and standard deviation 2.8 ± 2.0 years). 12 (71%) of all 17 dogs, were intact males, 2 (12%) were intact females and 3 (18%) were neutered males.

Grand mal seizures were noticed in all cases, 15 of them developed clusters of seizures and 8 dogs were presented with either survived or acute status epilepticus. In addition to generalized seizures in 5 dogs focal seizures and in 2 cases complex partial seizures were observed (table 2). Seizure frequency in these 17 dogs ranged from six epileptic seizures per month to one seizure every six months (table 14, appendix).

Table 2: Types of seizure in 29 dogs before treatment with AWD 131-138

	number of dogs	
type of seizure	**newly diagnosed**	**chronic epilepsy**
grand mal seizures	12/12	17/17
Cluster	5/12	15/17
status epilepticus	-	8/17
focal seizures	3/12	5/17
complex partial seizures	-	2/17

III.1.2 Dogs: retrospective study, conventional treatment

In the second part of this study, data from 82 well-documented cases with idiopathic epilepsy were analyzed retrospectively. The dogs were presented between 1999 and June 2001 at the Department of Small Animal Medicine and Surgery, School of Veterinary Medicine Hannover.

III.1.2.1 Newly diagnosed dogs

Seventy of these dogs had a newly diagnosed idiopathic epilepsy and were untreated prior to the presentation. All dogs had two or more seizures before treatment (table 12 and 13, appendix). Forty-four of these dogs were treated with phenobarbital with daily dosages ranging from 4 to 13 mg/kg bodyweight p.o. (median 5.0, mean and standard deviation 6.0 ± 2.4 mg/kg). Serum concentrations ranged between 4.6 – 33.2 µg/mL (median 17.2, mean and standard deviation 18.4 ± 7.2 µg/mL).

Twenty-six dogs were treated with primidone and received dosages from 24 to 70 mg/kg bodyweight p.o. (median 60.0, mean and standard deviation 51.0 ± 13.4 mg/kg). Serum concentrations of phenobarbital ranged between 5.9 – 37.5 µg/mL (median 18.3, mean and standard deviation 19.7 ± 10.2 µg/mL).

Forty different breeds (74%) and 18 mixed breed dogs (26%) were included. Breed distribution: Labrador Retriever (n=5), German Shepherd, Collie, Golden Retriever, Irish Setter (n=3), Border Collie, Saint Bernard, Weimaraner, Rhodesian Ridgeback, Shorthaired Dachshund each (n=2) and further different breeds (each n=1). 27 (39%) of them were males, 21 (30%) females, 13 (19%) neutered males and 9 (13%) dogs were neutered females (table 17 and 18, appendix).

The dogs ranged in an age from ¾ to 13 years (median age of 3.5 years, mean and standard deviation 4.2 ± 2.7 years). The pet owners recognized first seizures between an age of ½ to 12 years (median 2.5 years, mean and standard deviation 3.1 ± 2.3 years). All dogs had at least two or more seizures before treatment. In most of the dogs (n=61) generalized seizures (grand mal type) were observed. 19 dogs had clusters in the seizure history and 7 dogs were referred in the acute phase of status epilepticus or after recovery. 13 dogs had focal seizures and 3 dogs showed complex partial seizures (table 3).

III.1.2.2 Dogs with chronic epilepsy

Twelve dogs with chronic epilepsy had been treated with either phenobarbital or primidone for 3 months to 3 years (median 0.5 years, mean and standard deviation 1.7 ± 0.9 years) prior to presentation and did not respond to the medication. They received an additional drug, potassium bromide.

Eight of these dogs were treated with daily dosages of phenobarbital from 6 to 17 mg/kg bodyweight, p.o. (median 9.5, mean and standard deviation 10.0 ± 3.2 mg/kg), serum concentrations were measured and ranged from 18.7 to 41 µg/mL (median 24.6, mean and standard deviation 27.2 ± 8.4 µg/mL).

The remaining four dogs were treated with primidone at daily dosages from 50 to 70 mg/kg bodyweight p.o. (median 60.0, mean and standard deviation 60.0 ± 7.0 mg/kg). In these cases phenobarbital serum concentration ranged from 24.5 to 36.2 µg/mL (median 30.4, mean and standard deviation 30.4 ± 5.9 µg/mL).

Potassium bromide was administered at a daily dosage of 40 - 60 mg/kg bodyweight p.o. (median 41.0, mean and standard deviation 42.6 ± 5.4 mg/kg). Bromide concentration ranged from 0.6 to 1.4 mg/mL (median 0.9, mean and standard deviation 1.0 ± 0.3 mg/mL; therapeutic range 1.0 – 2.0 mg/mL, established by PODELL and FENNER 1993).

Nine (75%) different breeds and 3 (25%) mixed breed dogs were included. 2 (17%) of them were males, 2 (17%) females, 7 (58%) neutered males and 1 (8%) dog was a neutered female (table 20, appendix).

The dogs ranged in an age from 1 to 7 ½ years (median age of 2.3 years, mean and standard deviation 1.8 ± 1.1 years). The pet owners recognized first seizures between an age of ¾ to 5 years (median 1.6 years, mean and standard deviation 1.9 ± 1.3 years). In all dogs generalized seizures

(grand mal type) were observed. Seven dogs had clusters in the seizure history and six dogs were referred in the acute phase of status epilepticus or after recovery. Six dogs had focal seizures and in one dog complex focal seizures were described (table 3).

Table 3: Types of seizure in 82 dogs before treatment with phenobarbital or primidone in dogs with newly diagnosed idiopathic epilepsy or with chronic epilepsy (add on potassium bromide)

	number of dogs	
type of seizure	**newly diagnosed**	**chronic epilepsy**
grand mal seizures	61/70	12/12
Cluster	19/70	7/12
status epilepticus	7/70	6/12
focal seizures	13/70	6/12
complex partial seizures	3/70	1/12

III.2 Study design

III.2.1 Pilot study: AWD 131-138 treatment

The project was designed to be a prospective study over a period of 7 to 9 months, listed under the file number 509c-42502-00A19. In case of death the observation period was shorter (see results). History of the seizure frequency, severity and duration, age of onset of the first seizure and previous or ongoing antiepileptic treatment were recorded for each case (see III.1.1.). Epileptic seizures were categorized based on the owner's observations and video monitoring (table 2) (HEYNOLD et al. 1997,

BERNARDINI and JAGGY 1998, BERENDT and GRAM 1999, THOMAS 2000).

The diagnosis of idiopathic epilepsy was based on normal physical and neurologic findings and normal special examinations. All dogs had a standardized physical and neurological examination (JAGGY and TIPOLD 1999, see form 1, appendix). Blood work included in all cases hematology (red, white and differential cell count) and blood chemistry (alanine transferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), ammonia, glucose, urea, creatinine, total serum bilirubin, cholesterol, serum albumin, calcium, sodium and potassium). Plasma concentrations of phenobarbital (ALOMED, Radolfzell) were analyzed by an external laboratory. Further special examination were not performed in all dogs, but included analysis of the cerebrospinal fluid, computed tomography of the skull, EEG and X-ray of the thorax (table 4). In two cases idiopathic epilepsy was confirmed by histopathology at the Department of Pathology, School of Veterinary Medicine Hannover.

Table 4: Special examinations in 29 dogs treated with AWD 131-138

	number of dogs	
special examination	**newly diagnosed**	**chronic epilepsy**
computed tomography of the skull	8/12	9/17
cerebrospinal fluid	8/12	9/17
EEG	8/12	8/17
x-ray thorax	6/12	6/17

AWD 131-138 treatment started in all cases with a dosage of 5 mg/kg bodyweight p.o. twice a day for one week. In the second week the dosage was increased to 10 mg/kg in every dog. If seizures were still observed the dosage of AWD 131-138 was increased up to 30 mg/kg bodyweight twice a day (Table 5). The substance AWD 131-138 was applicated using 100 and 300 mg pills, which were analyzed before by elbion AG, Radebeul. To control different pharmaceutical parameters the pills were examined in regard of microbiology quality, content and pureness of AWD 131-138 (see appendix, form 2, certification of analysis).

Table 5: AWD 131-138 daily-dosage in mg/kg bodyweight

	number of dogs	
daily dosage	**newly diagnosed epilepsy: AWD 131-138 monotherapy**	**chronic epilepsy: AWD 131-138 add on treatment**
20 mg/kg	1/12	3/17
30 mg/kg	4/12	3/17
40 mg/kg	4/12	8/17
50 mg/kg	2/12	2/17
60 mg/kg	1/12	1/17

The first follow-up examination was performed three weeks after therapy with AWD 131-138 was started, followed by examinations at 6 or 8 week intervals or depending on individual occurrence of seizures. A clinical and neurological examination including blood work was done. During the study all owners kept a log book with precise description of occurring seizures, including frequency, duration and severity, behavioural changes, other

medication and possible observed adverse effects. At these time points the plasma concentration of AWD 131-138 and its metabolite were measured by VIATRIS GmbH & Co. KG, Frankfurt.
After the second month of treatment with the new substance AWD 131-138, a questionnaire (see appendix, form 4) was filled out by the owner focusing on seizure development and side effects: sedation, polyphagia, polyuria and polydipsia, vomiting, diarrhea, anorexia, attitude change, restlessness, augmented chewing after AWD-application, aggressiveness toward the owner or other dogs and gait abnormalities.

III.2.1.1 Measurement of plasma concentration of AWD 131-138

A pharmacokinetic study was performed at the beginning of treatment in 2 dogs with AWD 131-138 monotherapy and in 4 dogs with a combination therapy of AWD 131-138 and phenobarbital or primidone. All 6 dogs received 5 mg/kg bodyweight AWD 131-138. Blood was taken 3 times every 2 hours. The plasma concentration of AWD 131-138 and its metabolite were measured by VIATRIS GmbH & Co. KG, Frankfurt using HPLC/mass spectrometry. This method showed a high sensitivity and selectivity for AWD 131-138 and its metabolite AWD 47-111 (KNEBEL and DONATH 1998, unpublished data). The same method was used as a compliance control during the follow-up examinations. Blood was taken two and twelve hours after oral administration of AWD 131-138.

III.2.2 Retrospective study

The data obtained in this part of the study served as control. In all 82 cases with conventional medication (see III.1.2.) the history of seizure frequency, severity and duration, age of seizure onset and antiepileptic treatment was recorded for each case. Seizures were categorized based on the owner’s observations and video monitoring.

All dogs had a standardized physical and neurologic examination (JAGGY and TIPOLD 1999). Blood work performed in all dogs included hematology and blood chemistry (see III.2.1.). Serum concentrations of phenobarbital (ALOMED, Radolfzell) and potassium bromide (Gesellschaft für Epilepsieforschung E.V., Bielefeld) were analyzed by external laboratories. Other special examinations were not performed in all dogs and included computed tomography of the skull, examination of the cerebrospinal fluid, EEG and X-ray of the thorax (table 6).

Table 6: Special examinations in 82 dogs (retrospective study)

	number of dogs	
special examination	**newly diagnosed**	**chronic epilepsy**
computed tomography of the skull	22/70	5/12
cerebrospinal fluid	22/70	5/12
EEG	27/70	9/12
x-ray thorax	36/70	8/12

If all examinations performed were within normal limits idiopathic epilepsy was suspected, respectively diagnosed. The pet owners were asked about clinical observations, treatment outcome in respect to seizure frequency, duration and severity before and after treatment, which included a period between 1 and 9 months.

III.2.3 Statistics

The statistical software package WinSTAT® for EXCEL® was used to calculate descriptive parameters in each group such as mean, median value and standard deviation of age, age of seizure onset, age at the beginning of treatment, the dosages of phenobarbital, primidone or potassium bromide including the serum concentration. The significance of differences between seizure frequency before and during treatment were calculated by the Wilcoxon Signed Rank test for paired replicates using InStat®. The level of significance was chosen as P = 0.05. Comparison of treatment groups were performed by ANOVA (3 groups) or Fisher´s exact test (2 groups).

IV Results

IV.1 Seizure frequency

IV.1.1 Pilot study: AWD 131-138 treatment

IV.1.1.1 Newly diagnosed dogs

Prior to presentation seizure frequency ranged from eight seizures per month to one seizure every eight months (median 1.6). During monotherapy with AWD 131-138 seizure frequency per month varied from complete control of seizures to 9 seizure events per month (median 0.71) (table 7). However, the improvement was not statistically significant. In 9 of these 12 dogs a seizure reduction was observed. Calculating the values in these nine dogs and therefore eliminating the non-responders the median seizure frequency per month was 1.7 before treatment and 0.55 during AWD 131-138 medication. The improvement of seizure frequency in these dogs was statistically significant ($p<0.05$). The percentage of seizure reduction in responders was 49,8 % given as mean value (table 7).

One dog (8%), which was seizuring 5 times before treatment remained seizure free for the observation period of 9 months (according to new information of the owner he is now seizure free for 17 months). A reduction of seizure frequency by more than 50% was achieved in four of twelve dogs (33%) (table 7). 3 dogs (25%) were considered as non-responders defined as dogs either showing no decrease in seizure frequency or an increase in seizure frequency during treatment. One of these 3 animals died in status epilepticus 2 months after the first medication receiving a dosage of 30 mg/kg AWD 131-138 and having a measured plasma concentration of 3997.5 ng/mL 2 hours after application. One dog worsened, but improved after supplementation with phenobarbital.

Comparison of monotherapy treatment groups (IV.2.1. - IV.2.2.) by ANOVA did not indicate any significant differences between the antiepileptic efficacy of AWD 131-138, phenobarbital or primidone.

IV.1.1.2 Dogs with chronic epilepsy and add-on treatment with AWD 131-138

The seizure frequency per month varied during unsuccessful treatment with phenobarbital or primidone from eight seizures per month to one respectively four seizures every six months (median 1.9). During the add-on treatment with AWD 131-138 seizure frequency per month ranged from free of seizures to 9 seizure events (median 2.0) (table 8). In 10 of these 17 dogs a seizure reduction was observed. Calculating the values in these ten dogs and therefore eliminating the non-responders the median seizure frequency per month was 2.4 before treatment and 1.1 during supplementation with AWD 131-138. The improvement of seizure frequency in these dogs was statistically significant ($p<0.05$). The percentage of seizure reduction in responders was 47,2 % given as mean value (table 8).

6 dogs (35 %) had a seizure reduction of more than 50 %. One dog (6 %) was completely free of seizures. This dog started seizuring at an age of 8 ½ years with 1 to 4 clusters per month. After 3 months of combined therapy with AWD 131-138 he was euthanized unfortunately because of acute leukemia. Two other dogs had still 2 seizures at the beginning of the treatment, but were free of seizures for the rest of the nine months observation period. The remaining 11 dogs had a seizure reduction under 50 % (4 dogs) or were considered to be non-responders (7 dogs). Nine patients in this group either died or were euthanized in status epilepticus on the owners request. Two of them were examined histopathologically. No extraneural or neural lesions were detected. Another dog died after

coumarin intoxication. In these dogs the treatment observation period was reduced to 2 to 8 months.

IV.1.2 Retrospective study, conventional treatment

IV.1.2.1 Newly diagnosed dogs, phenobarbital monotherapy

Prior to treatment seizures occurred with a frequency from seven per month to one seizure every six months (median 1.6) (table 7). Seizure frequency per month during therapy with phenobarbital ranged from free of seizures to 10 seizure events (median 0.59). The seizure reduction was statistically significant. In 32 of these 44 dogs a seizure reduction was observed. Calculating the values in these 32 dogs and eliminating the non-responders the median seizure frequency per month was 1.68 before treatment and 0.42 during the medication with phenobarbital. The improvement of seizure frequency in these dogs was also statistically significant ($p<0.05$). The percentage of seizure reduction in responders was 72.4 % given as mean value (table 7).

Nine (20%) out of these 44 dogs were free of epileptic seizures during the treatment. In 28 (64%) dogs a seizure reduction of more than 50% was observed. Twelve dogs (27 %) were considered to be non-responders. 10 dogs of this group either died or were euthanized in status epilepticus on the owners request. 3 additional dogs were euthanized because of other diseases than epilepsy.

IV.1.2.2 Newly diagnosed dogs, primidone monotherapy

In these 26 dogs seizures occurred with a frequency from ten per month to one seizure every five months (median 1.75) (table 7). During primidone treatment seizure events per month ranged from 0 to 12 (median 0.39). However, this seizure reduction was not statistically significant. In 19 of 26 dogs a seizure reduction was observed. Calculating the values in these 19 dogs and eliminating the non-responders the median seizure frequency per month was 2.0 before treatment and 0.29 during the medication with primidone. The improvement of seizure frequency in these dogs was statistically significant ($p<0.05$). The percentage of seizure reduction in responders was 75.1 % given as mean value (table 7).

Four dogs (15%) were free of seizures under primidone treatment. In sixteen dogs (62%) the reduction of seizure frequency was higher than 50%. Seven dogs (27%) were considered to be non-responders. 10 dogs of this group either died or were euthanized in status epilepticus on the owners request.

IV.1.2.3 Dogs with chronic epilepsy and add-on treatment with potassium bromide

In twelve dogs not responding to phenobarbital or primidone medication was supplemented with potassium bromide. Seizures occurred with a frequency from 13 per month to one seizure every second month (median 3.0). During the combination therapy seizure frequency varied from 11 per month to one seizure every eight months (median 1.9) (table 8), a seizure reduction which was not statistically significant. In 7 of 12 dogs a seizure reduction was observed. Calculating the values in these 7 dogs and therefore eliminating the non-responders the median seizure frequency per month was 3.0 before treatment and 0.8 during the add-on

treatment with potassium bromide. The improvement of seizure frequency in these dogs was statistically significant ($p<0.05$). The percentage of seizure reduction in responders was 59.7 % given as mean value (table 8). In 5 dogs (42%) the reduction of seizure frequency was higher than 50%, 5 further dogs were considered to be non-responders. 6 dogs of this group either died or were euthanized in status epilepticus on the owners request.

Comparison of treatment groups in dogs with chronic epilepsy by Fisher´s exact test did not indicate any significant difference between the antiepileptic efficacy of the two add-on treatment schedules (see table 8).

Table 7: Effect of monotherapy with AWD 131-138, phenobarbital or primidone in epileptic dogs

Non-responders were defined as dogs either showing no decrease in seizure frequency or an increase in seizure frequency during treatment. Seizure frequencies are given as median group values, percent reduction of seizures is given as mean ± SEM (standard error of mean). „n" is the number of epileptic dogs per group. Significant differences in values before and during treatment are indicated by asterisk (P<0.05). Comparison of treatment groups by ANOVA did not indicate any significant difference between the antiepileptic efficacy of the three drugs.

	AWD 131-138			**Phenobarbital**			**Primidone**		
	n	before treatment	during treatment	n	before treatment	during treatment	n	before treatment	during treatment
Seizure frequency (seizures/month)									
All dogs	12	1.6	0.71	44	1.6	0.59*	26	1.75	0.39
Without nonresponders	9	1.7	0.55*	32	1.68	0.42*	19	2.0	0.29*
% reduction of seizures in responders	9		49.8±11.3	32		72.4±4.6	19		75.1±5.1
Number of dogs with >50% reduction of seizures			4/12 (33%)			28/44 (64%)			16/26 (62%)
Number of seizure-free dogs			1/12 (8%)			9/44 (20%)			4/26 (15%)
Number of nonresponders			3/12 (25%)			12/44 (27%)			7/26 (27%)

Table 8: Dogs with chronic epilepsy, add-on therapy with AWD 131-138 or potassium bromide

Non-responders were defined as dogs either showing no decrease in seizure frequency or an increase in seizure frequency during treatment. Seizure frequencies are given as median group values, percent reduction of seizures is given as mean ± SEM (standard error of mean). „n" is the number of epileptic dogs per group. Significant differences in values before and during treatment are indicated by asterisk (P<0.05). Comparison of treatment groups by Fisher's exact test did not indicate any significant difference between the antiepileptic efficacy of the two drugs.

	Phenobarbital/Primidone AWD 131-138			**Phenobarbital/Primidone Potassium bromide**		
	n	before treatment	during treatment	n	before treatment	during treatment
Seizure frequency (seizures/month)						
All dogs	17	1.9	2.0	12	3.0	1.9
Without non-responders	10	2.4	1.1*	7	3.0	0.8*
% reduction of seizures in responders	10		47.2±8.8	7		59.7±5.9
Number of dogs with >50% reduction of seizures			6/17 (35 %)			5/12 (42%)
Number of seizure-free dogs			1/17 (6 %)			0/12
Number of non-responders			6/17 (35%)			5/12 (42%)

IV.2 Duration and severity of seizure activity

IV.2.1 Pilot study: AWD 131-138 treatment

IV.2.1.1 Newly diagnosed dogs

In this group of dogs the duration of the ictus prior to presentation varied from half a minute to 10 minutes (median 3.0 minutes) (table 9). The average time in most patients was 2 to 3 minutes. During monotherapy with AWD 131-138 ictus duration ranged also from half a minute to 10 minutes but with a median value of 2.5 minutes. In five cases the duration of the ictus was decreased between 12 and 50% (mean 38%).
A postictal phase with behaviour changes was observed in all twelve dogs before presentation and ranged between 10 minutes to 24 hours. In four dogs the postictal time was shortened for 50 to 75%.

A decrease of seizure severity was described subjectively by nine of 12 owners. Prior to presentation all dogs had grand mal seizures (table 2), which extended in five dogs to clusters. During AWD 131-138 treatment two dogs only developed focal seizures. One dog never got clusters, the other 4 dogs had a reduced seizure number per cluster (mean 45.3 % reduction).

IV.2.1.2 Dogs with chronic epilepsy and add-on treatment with AWD 131-138

Grand mal seizure duration in seventeen dogs during the conventional monotherapy with phenobarbital or primidone ranged from 30 seconds to 10 minutes (median 2.0 minutes) (table 9). After supplementation with AWD 131-138 duration of seizures was slightly diminished from 30 seconds to 5 minutes with a median of 2.0 minutes. The time of the ictus was decreased in 3 dogs from 40 to 50%.

A postictal phase with behavior changes was observed in all dogs before presentation and ranged between 30 minutes to 48 hours (mean 8.5 hours). During AWD 131-138 treatment the range of this time was 10 minutes to 24 hours (mean 5.5 hours) since in ten dogs it was shortened for 30 to 75% (mean 54%).

In eight of seventeen cases the pet owners described subjectively a decrease of seizure severity. All seventeen dogs had prior to AWD 131-138 treatment grand mal seizures, which expanded into clusters in 15 dogs and/or into status epilepticus in 8 dogs (table 2). After additional AWD 131-138 application in nine dogs focal seizures replaced grand mal seizures partially. In three dogs clusters did not occur anymore and the number of seizures per cluster decreased in additional 4 cases between 21 and 64% (mean 39,5%). One owner reported worsening of seizure severity and stopped abruptly the application of AWD 131-138 after two months of treatment without further side effects to the dog. In another dog the AWD-application was reduced gradually on the owners request after 4 months treatment without complications.

IV.2.2 Retrospective study, conventional treatment

IV.2.2.1 Newly diagnosed dogs, phenobarbital monotherapy

The duration of the ictus before treatment varied from 0.5 to 10 minutes (median 4.0 minutes) (table 9). The average time in most cases was 2 to 3 minutes. During phenobarbital application the duration of the main seizure episodes varied also from 0.5 minutes to 10 minutes but with a median value of 5.0 minutes. In only 4 dogs, which did not become seizure free, a shortening of the observed ictus from 33 to 50% occurred.
A postictal phase with behavior changes was observed in 39 dogs before treatment and ranged between ten minutes to twenty-four hours (mean

3.5 hours). During phenobarbital application the postictal phase was reduced to 5 minutes to 24 hours (mean 3 hours). This time period was abbreviated in 8 dogs from 30 to 65% (mean 43%).

In 24 cases, which did not become seizure free, the owner reported subjectively a decrease of seizure severity. Before the presentation 40 dogs had grand mal seizures, which expanded in ten cases into clusters, in four dogs into status epilepticus (table 3). During phenobarbital medication in 6 dogs focal seizures instead of grand mal seizures were observed by the owner. In 3 out of ten dogs cluster development stopped. In 3 out of 4 dogs status epilepticus did not occur anymore. In 11 dogs the grand mal seizure activity remained unchanged or severity increased according to the owners record.

IV.2.2.2 Newly diagnosed dogs, primidone monotherapy

In these twenty-six dogs the ictus prior presentation ranged from 0.5 minutes to 10 minutes (median 1.5 minutes) (table 9). In most cases the average time was 2 to 3 minutes. During primidone therapy ictus duration varied from 0.5 minutes to 10 minutes (median of 1.0 minutes) and decreased only in 2 dogs (30%).
Postictal signs were observed in twenty-two dogs before presentation and ranged between 15 minutes to 48 hours (mean 5 hours). During primidone application the postictal phase lasted for 10 minutes to 48 hours (mean 4.5 hours). The duration of the postictal phase was shortened in 5 dogs from 25 to 65% (mean 40%).

In ten of 22 cases, which did not become seizure free, the owner reported subjectively a decrease of seizure severity. Before treatment 25 dogs had grand mal seizures, which expanded in nine cases into clusters, in three

dogs into status epilepticus (table 3). During primidone application in 2 dogs focal seizures instead of grand mal seizures were observed by the owner. In 5 out of ten dogs the frequency of seizures per cluster was reduced between 23 and 50% (mean 37,5%). Status epilepticus was not observed anymore in all 3 dogs. In 2 dogs seizure severity increased according to the owners record.

IV.2.2.3 Dogs with chronic epilepsy and add-on treatment with potassium bromide

In the twelve dogs treated with phenobarbital or primidone monotherapy ictus duration varied from 1.0 minute to 13 minutes (median 3.0 minutes) (table 9). The average time in most cases was 1 to 3 minutes. After potassium bromide supplementation the duration of the ictus varied from 1.0 minute to 10 minutes (median 2.0 minutes). The duration of the ictus decreased in 3 dogs from 40 to 50%.
Postictal signs were observed in eleven dogs before presentation and ranged between half an hour to 24 hours (mean 6.0 hours). During combination therapy with potassium bromide the postictal phase varied from 15 minutes to 24 hours (mean 5.5 hours). The duration of postictal phase was abbreviated in two dogs (50 and 75%).

In 4 of twelve cases the owner reported a decrease of seizure severity subjectively. Prior to the combination therapy all twelve dogs had grand mal seizures which developed into status epilepticus in six dogs and in seven dogs into clusters, which did not occur anymore after supplementation with potassium bromide in 6 dogs. In one dog the owner noticed an increase of seizure severity.

Table 9: Duration of the ictus during grand mal seizure activity before and during different anticonvulsive treatment methods

treatment	**duration** before treatment	**duration** during treatment
monotherapy AWD 131-138 (n=12)	3.0[1] (0,5-10)[2]	2.5[1] (0.5-10)[2]
add-on therapy phenobarbital or primidone and AWD 131-138 (n=17)	2.0[1] (0.5-10)[2]	2.0[1] (0.5-5)[2]
monotherapy phenobarbital (n=44)	4.0[1] (0.5-10)[2]	5.0[1] (0.5-10) [2]
monotherapy primidone (n=26)	1.5[1] (0.5-10)[2]	1.0[1] (0.5-10)[2]
add-on therapy phenobarbital or primidone and potassium bromide (n=12)	3.0[1] (1-13)[2]	2.0[1] (1-10)[2]

Table legend: n = number of dogs; median values[1] and time range[2] expressed in minutes

IV.3 Plasma concentrations of AWD 131-138

In six dogs entering the pilot study with AWD 131-138 a pharmacokinetic study was performed. AWD 131-138 was measured in plasma samples two, four and six hours after application. The results are summarized in table 10. The initial dosage of AWD 131-138 was 5 mg/kg bodyweight p.o. in all cases.

Table 10: AWD 131-138 plasma concentration in ng/mL

time after application	2 hours	4 hours	6 hours
AWD 131-138 monotherapy			
dog 1	720.0	702.7	229.5
dog 2	2579.2	1461.0	709.0
AWD 131-138 phenobarbital combination therapy			
dog 3	23.27	bld	bld
dog 4	1019.5	173.8	19.5
AWD 131-138 primidone combination therapy			
dog 5	1520.5	1021.5	448.1
dog 6	2392.3	2438.7	1289.0

Table legend: AWD 131-138: bld (below limit of detection): < 2 ng/mL

IV.3.1 AWD 131-138 plasma concentration in newly diagnosed dogs

To control the compliance of the owner AWD 131-138 plasma concentration were measured for the first time three weeks after the beginning of the treatment 2 and 12 hours after application. The concentration ranged in eleven cases 2 hours after oral application between 53.28 and 8619.4 ng/mL (median 2585.0, mean and standard deviation 3356.3 ± 3290.3 ng/mL) (figure 3 and 4). The AWD 131-138 dosage varied between 10 mg/kg bodyweight in eight dogs, 15 mg/kg bodyweight in two dogs and 20 mg/kg bodyweight twice a day in one dog. Plasma concentrations at this time point 12 hours after application ranged

in all twelve dogs between 5.4 and 1139.2 ng/mL (median 218.1, mean and standard deviation 377.5 ± 406.0 ng/mL) (figure 3). Further control examinations were performed at different time points in each dog. The plasma concentrations varied between 53.28 and 10 737.41 ng/mL two hours after oral application (figure 3 and 5). There was no correlation between plasma concentration and seizure frequency (figure 4 and 5).

IV.3.2 AWD 131-138 plasma concentration in dogs with chronic epilepsy

The plasma concentration of the seventeen dogs with chronic epilepsy and add-on treatment ranged between 279.6 to 10613.7 ng/mL (median 2992.4, mean and standard deviation 3896.1 ± 3339.2 ng/mL) after 2 hours of application (figure 4). The AWD 131-138 dosage varied between 10 mg/kg bodyweight in fifteen dogs and 15 mg/kg bodyweight in two dogs twice a day. Plasma concentration after 12 hours of application ranged between 7.57 and 5873.04 ng/mL (median 179.3, mean 644.0). Further control examinations were also performed in this group at different time points. The plasma concentrations varied between 156.46 and 26 710.58 ng/mL two hours after oral application (figure 3). However, the therapeutic range of AWD 131-138 is not known until this time point. There was no correlation between plasma concentration and seizure frequency (figure 4 and 5).

Figure 3: **AWD 131-138 plasma concentration measured 2 and 12 hours after oral application from 20-30 mg/kg AWD 131-138 (monotherapy)**

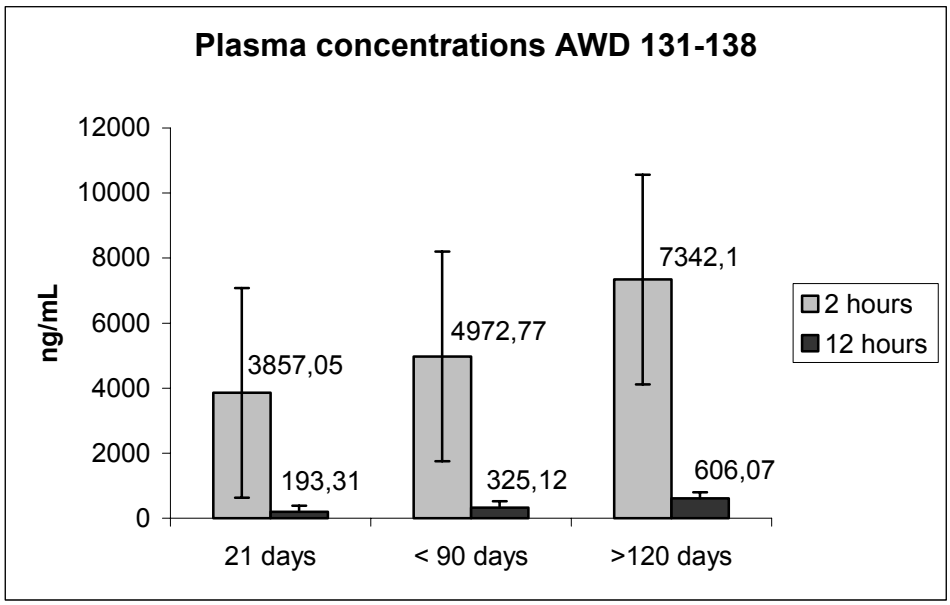
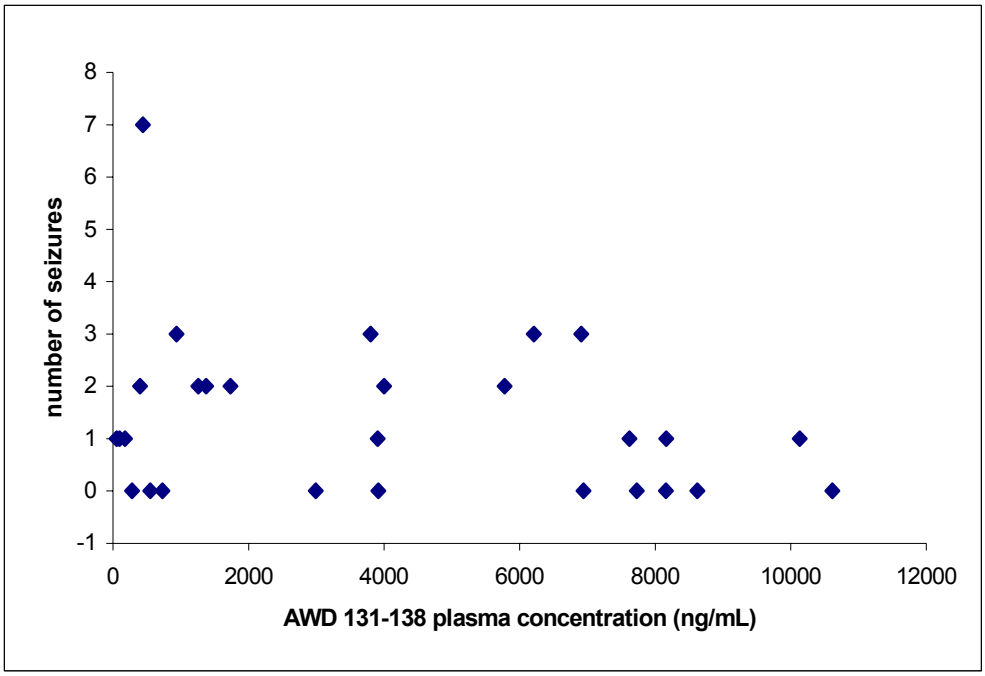


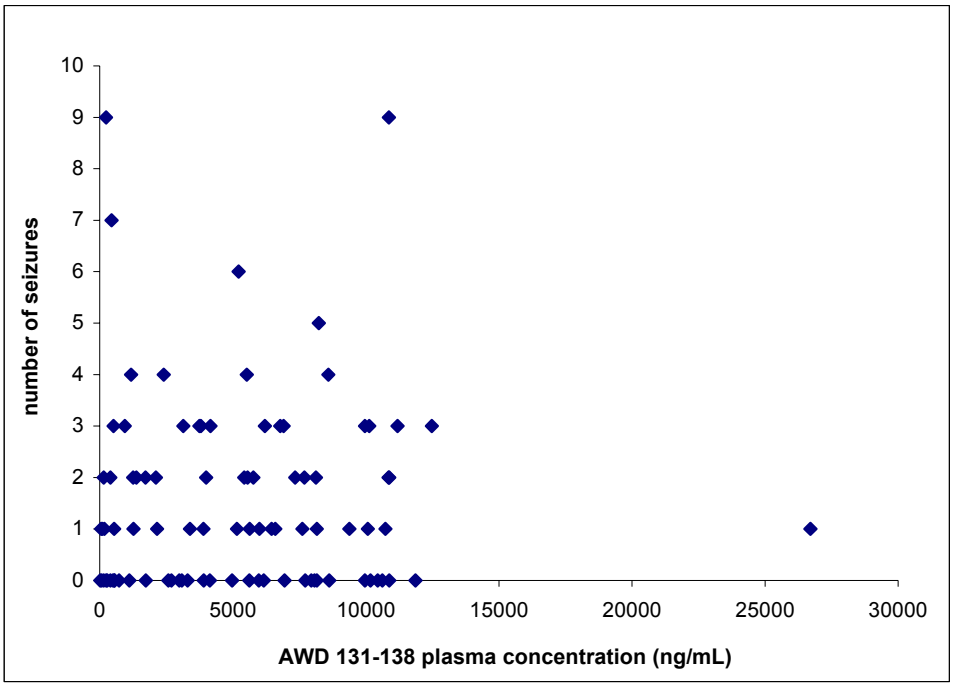
Figure legend: The plasma concentrations are given as median values and standard deviation. The measurements took place 21 days after treatment start and on different time points during the treatment period (between 30 and 90 days (< 90 days) and >120 days).

Figure 4: AWD 131-138 plasma concentration (ng/mL) and number of seizures during the first month of treatment (2 h post application) in dogs with newly diagnosed and chronic epilepsy



No correlation between seizure frequency and plasma concentration occurred.

Figure 5: AWD 131-138 plasma concentration (ng/mL, 2 h post application) and number of seizures during follow up examinations in dogs with newly diagnosed idiopathic epilepsy



No correlation between seizure frequency and plasma concentration occurred.

IV.4 Evaluation of the questionnaire in AWD 131-138 treated dogs

After two months of treatment with the new substance all owners had to fill in a questionnaire (see form 4, appendix).

IV.4.1 Evaluation of the questionnaire: AWD 131-138 application in 12 dogs with newly diagnosed idiopathic epilepsy

The main side effect in the twelve dogs treated with AWD 131-138 observed by the owners was polyphagia which occurred in 7 (58%) cases, in 4 dogs only at the beginning of the study. No further side effects were seen.

IV.4.2 Evaluation of the questionnaire: AWD 131-138 application in 17 dogs with chronic epilepsy

The main side effect observed by the owner in the seventeen dogs treated with conventional antiepileptic drugs supplemented with AWD 131-138 was polyphagia which occurred in 10 (59%) cases, in 7 dogs only at the beginning of the study. Two dogs with combined phenobarbital treatment and high levels of phenobarbital serum concentrations (56,6 - 58,9 µg/mL) showed ataxia in the hind limbs and apathy 2-4 hours after AWD 131-138 application with dosages from 40 mg/kg AWD 131-138 bodyweight per day and plasma concentrations from 5563,26 to 10858,45 ng/mL after 2 hours of application. In one of these dogs augmented chewing was observed after AWD-application. No further side effects were seen.

IV.4.3 Follow up: AWD 131-138 application in 12 dogs with newly diagnosed idiopathic epilepsy

During regular follow up examinations clinical and neurological examinations remained normal. One dog received from the referring veterinarian enrofloxacin because of intestinal infection and started seizuring after 24 hours. After removing this medication no further seizures were observed. No abnormalities were found in hematology (red, white and differential cell count) and blood chemistry.

IV.4.4 Follow up: AWD 131-138 application in 17 dogs with chronic epilepsy

During regular follow up examinations clinical and neurological examinations remained normal in 15 dogs. In two of the dogs with combined phenobarbital treatment the ataxia observed already by the owners could be verified. The two dogs had slight proprioceptive deficits in all 4 legs, but only 2-4 hours after AWD 131-138 application. After this time point the dogs were clinically normal. One dog received penicillin-streptomycin because of pulmonary infection by the referring veterinarian and became apathic after the medication. Removing this additional medication resulted in sudden improvement.

No abnormalities were found in hematology (red, white and differential cell count). Blood chemistry revealed abnormalities already at the beginning of the study and during the add-on treatment. An elevation of the AP occurred in 6 dogs, of ALT in 1 dog and of GLDH in 3 dogs. All other parameters examined remained in the normal range.

V Discussion

AWD 131-138, a new antiepileptic and anxiolytic drug, was evaluated in this clinical pilot study in dogs with newly diagnosed or chronic idiopathic epilepsy to verify the anticonvulsant effectiveness of this substance, which could be shown experimentally before (LÖSCHER and POTSCHKA, 1998a and b, unpublished data). Dogs with idiopathic epilepsy represent the only genetic and naturally occurring animal model of epilepsy (LÖSCHER 1984 and 1986). Similar to human epilepsy animals may be selected into dogs with pharmacoresistant seizures and dogs with pharmacosensitive seizures (LÖSCHER, 1997). Therefore and because of strong clinical similarity the dog represents an ideal tool to study the efficacy of antiepileptic drugs (LÖSCHER, 1984).

In the present study the data obtained from dogs treated with AWD 131-138 were compared to results from dogs with conventional antiepileptic medication. To enter the study all dogs had to fulfill the following main criterias: normal clinical and neurological examination, no abnormalities in special examinations and two or more seizures before the beginning of treatment. In dogs with chronic epilepsy the phenobarbital serum concentrations had to be in the therapeutic range. To get a broad range of epileptic dogs, animals were not selected because of breed, age, seizure type and seizure frequency. Therefore different breeds and mixed breed dogs were included. However, large breed dogs such as the German Shepherd or Retrievers were overrepresented reflecting the well known fact that large breed dogs (>15kg) are significantly more affected with idiopathic epilepsy than small breed dogs (PODELL et al. 1995).

The majority of dogs included in all parts of the study - in AWD 131-138 treatment as well as in the retrospective evaluation of conventional medication - was seizuring for the first time between the first and third

year of live. Several authors describe that idiopathic epilepsy mostly begins in this period (OLIVER 1987, OLIVER and LORENZ 1993, CHRISMAN 1991, DE LAHUNTA 1983, MARTINEK and HORAK 1970, CROFT 1965 and 1971, CENTER 1986, CUNNINGHAM 1971, SCHWARTZ-PORSCHE 1984 and FORRESTER et al. 1989). In the present study a part of the dogs started seizuring with an age younger or older than 1 to 3 years. In nearly all groups one old dog entered the study with the clinical diagnosis of idiopathic epilepsy and normal clinical and special examinations. Even the diagnosis might be questionable because of the old age, these dogs fulfilled the criteria for this study and added information to the broad aspects of a clinical pilot study.

To receive information about the ideal dosage of AWD 131-138 in naturally occurring canine idiopathic epilepsy all dogs started with 5 mg/kg bodyweight p.o. twice a day for one week according to previously performed studies (LÖSCHER and POTSCHKA, unpublished data a and b, 1998). This dosage was doubled in every dog after the second week. In animals which did not respond the dosage was increased up to 30 mg/kg bodyweight p.o. twice a day. In single cases with rapid increase of the dosage no side effects were observed and it seems possible that high dosages can be used at treatment start. Different dosages modified according to the treatment response were also used in the group with conventional medication. Therefore the different treatment schedules are comparable.

Plasma concentrations of AWD 131-138 were measured for two purposes: to control pharmacokinetics after a single dose of oral application of the new substance in affected dogs and to control the owners compliance during the study. Pharmacokinetics revealed a high variation of plasma concentrations, probably caused by the different distribution of the substance in different tissues (KRONE, unpublished data, 1998). The same

variability in plasma concentrations also occurred after 3 weeks of the medication with AWD 131-138 and at different time points. An interesting finding was that in dogs with chronic epilepsy and treatment with phenobarbital supplemented with AWD 131-138 the lowest values were found. Further studies should be performed to evaluate, if a certain interaction between phenobarbital and AWD 131-138 occurs leading to low plasma concentrations. Plasma concentration did not correlate with the seizure frequency. However, in dogs with slow increase of the AWD 131-138 dosage seizure reduction occurred only with a certain delay. Since no side effects were observed a more aggressive treatment schedule could be introduced in future experiments and enhance the effectiveness in dogs with idiopathic epilepsy.

Reduction of seizure frequency using AWD 131-138 in dogs with newly diagnosed idiopathic epilepsy was comparable with the reduction in dogs treated either with phenobarbital or primidone. The results of the present retrospective evaluation of phenobarbital and primidone treatment outcome concur with previously described studies (SCHWARTZ-PORSCHE et al. 1985). The three treatment groups did not indicate any significant difference between the antiepileptic efficacy of the three drugs. Calculating the reduction of the seizure frequency excluding the non-responders revealed in all three groups significant differences in values before and during treatment. In the AWD 131-138 treated group total percentage of seizure reduction was somewhat lower than in the other groups. However, the number of patients in the prospective pilot study group was lower than in the retrospective group and might influence the outcome. Higher dosages of AWD 131-138 at the beginning of a treatment schedule could further improve the anticonvulsive effectiveness of the new substance.

In dogs with chronic epilepsy and add-on therapy with either AWD 131-138 or potassium bromide the supplementation with another substance had an effect on the seizure frequency. Dogs improved to a similar degree in both groups. Calculating the reduction of the seizure frequency excluding the non-responders revealed in both groups significant differences in values before and during treatment. The percentage of non-responders was higher than in dogs with newly diagnosed epilepsy as expected.

In addition to the reduction of seizure frequency, seizure duration and severity before and during treatment was evaluated. During AWD 131-138 medication the ictus of grand mal seizures was shortened in more than 1/3 of the cases. This phenomenon did only rarely occur in phenobarbital treated dogs (about 1/10 of the dogs). In contrary, in phenobarbital treated dogs the median values of ictus duration increased during the medication. However, the postictal phase was shortened in all groups examined. In addition to the shortening of the ictus and the postictal phase the severity of single seizure events was reduced during AWD 131-138 treatment. Grand mal seizures changed into focal seizures, the occurrence of clusters disappeared or the number of single seizures per cluster was reduced. Most of the owners described subjectively a decrease of seizure severity.

The most obvious difference between AWD 131-138 treatment and the conventional medication occurred evaluating side effects. Side effects were only rarely reported and included polyphagia at the beginning of the treatment and ataxia in two dogs with combined phenobarbital treatment and high phenobarbital serum concentrations. The described severe side effects reported in phenobarbital treatment such as polydipsia, polyphagia, excessive sedation and gait abnormalities (BUNCH et al. 1982, SCHWARTZ-PORSCHE et al. 1985) did not occur. The ataxia in the

mentioned dogs was probably caused by the combination with phenobarbital. The side effects of phenobarbital treatment are sometimes not acceptable for the owners and the therapy is stopped. Using AWD 131-138 the compliance of the owners was extremely good, especially because the dogs never showed any sedation. Chronic application of primidone and phenobarbital may lead to considerable elevation of liver enzymes (SCHWARTZ-PORSCHE et al. 1985), which was not observed in dogs treated with AWD 131-138 monotherapy and is considered to be a big advantage for the interpretation of laboratory results in possibly occurring other diseases than epilepsy.

In summary the present pilot study confirms that the new substance AWD 131-138 has a potent anticonvulsant effect in dogs with idiopathic epilepsy. AWD 131-138 is equipotent to conventional antiepileptic drugs such as phenobarbital or primidone. Chronic administration is well tolerated and less side effects were observed in comparison to traditional antiepileptic drugs. Further prospective studies with higher numbers of epileptic dogs treated with AWD 131-138 have to confirm this pilot study. These studies should also provide the answer, if higher dosages at the beginning of the treatment will enhance the success rate. Interaction with other drugs have to be considered and noted.

VI Summary

Susanne Rieck

Clinical pilot study with a new antiepileptic substance in dogs with idiopathic epilepsy

In this prospective clinical pilot study a new antiepileptic and anxiolytic drug, AWD 131-138, was evaluated in twenty-nine dogs with newly diagnosed or chronic idiopathic epilepsy to verify the anticonvulsant effectiveness of this new substance which could be shown experimentally before.

Dogs with idiopathic epilepsy represent the only genetic and naturally occurring animal model of epilepsy. Similar to human epilepsy animals may be selected into dogs with pharmacoresistant seizures and dogs with pharmacosensitive seizures. Therefore and because of strong clinical similarity the dog represents an ideal tool to study the efficacy of antiepileptic drugs. In dogs only a few antiepileptic drugs can be used succesfully as a life long treatment and in about one third of the cases pharmacoresistency is observed. The need for new antiepileptic drugs for dogs is obvious.

In the present study the data obtained from 29 dogs treated with the new antiepileptic substance AWD 131-138 were compared to results from 82 dogs with conventional antiepileptic medication (phenobarbital, primidone and add-on treatment with potassium bromide) obtained retrospectively.

To enter the study all dogs had to fulfill the following criterias: normal clinical and neurological examination, no abnormalities in special examinations and two or more seizures before beginning of treatment. In

dogs with chronic epilepsy the phenobarbital serum concentrations had to be in the therapeutic range. In all cases seizure frequency, duration and severity were analyzed.

Reduction of seizure frequency using AWD 131-138 in twelve dogs with newly diagnosed idiopathic epilepsy was comparable with the reduction in 70 dogs treated either with phenobarbital or primidone. Comparison of treatment groups by ANOVA did not indicate any significant difference between the efficacy of the three drugs AWD 131-138, phenobarbital and primidone.

In 29 dogs with chronic epilepsy and add-on therapy with either AWD 131-138 in seventeen or potassium bromide in twelve dogs the supplementation with another substance had an effect on the seizure frequency. Dogs improved to a similar degree in both groups.

In addition to the reduction of seizure frequency, during the AWD 131-138 medication the seizure duration and severity were affected. The ictus of grand mal seizures was shortened in more than one third of the cases. In contrary, in phenobarbital treated dogs the median values of ictus duration increased during the medication.

The most obvious difference between treatment with the new substance AWD 131-138 and the conventional medication occurred evaluating side effects which were only rarely reported.

In summary the present pilot study confirms that the new substance AWD 131-138 has a potent anticonvulsant effect in dogs with idiopathic epilepsy. AWD 131-138 is equipotent to conventional antiepileptic drugs such as phenobarbital or primidone. Chronic oral administration is well tolerated and less side effects were observed in comparison to traditional antiepileptic drugs.

VII Erweiterte Zusammenfassung

Susanne Rieck

Klinische Pilotstudie zur Prüfung einer neuen antiepileptischen Wirksubstanz an Hunden mit idiopathischer Epilepsie

Epilepsien stellen bei Mensch und Wirbeltier die häufigsten neurologischen Erkrankungen des Gehirns dar, insbesondere Hund und Katze sind betroffen (OLIVER 1980, SCHWARTZ-PORSCHE 1984, LÖSCHER et al. 1985, FREY 1989). Sie treten beim Menschen und beim Hund mit einer Prävalenz von 0,5-1% auf (US Department of Health, Education and Welfare 1977, JANZ 1979, LÖSCHER et al.1985, KERÄNEN und RIEKKINGEN 1988, FORRESTER et al. 1989, SRENK et al. 1994).

Unter dem Begriff Epilepsie wird eine Vielzahl von Krankheiten und Syndromen zusammengefasst, deren Gemeinsamkeit ein plötzliches Auftreten von vorübergehenden (paroxysmalen), spontanen Entladungen einzelner Nervenzellen, Neuronengruppen oder des gesamten Großhirns ist (LÖSCHER 1993, JAGGY und STEFFEN 1995a). Wenn keine anfallsauslösenden Ursachen, wie Läsionen im zentralen Nervensystem (ZNS) oder extraneurale Störungen, die das Gehirn sekundär beeinflussen, nachweisbar sind, liegt die idiopathische, genuine oder genetische Form der Epilepsie vor. Im Unterschied dazu setzt bei der erworbenen, symptomatischen Form eine pathologische Veränderung die Krampfschwelle herab und provoziert klinische Anfälle (JAGGY und STEFFEN 1995a).

Bei ca. 45 % der Hunde mit Anfallsleiden wird die idiopathische Epilepsie im Ausschlussverfahren diagnostiziert (PODELL et al. 1995; JAGGY und

STEFFEN 1995 a und c). Bei dieser Form der Epilepsie treten beim Hund in 80-90% der Fälle vornehmlich generalisierte tonisch-klonische Anfälle auf, die mit Bewusstseinsverlust einhergehen (Grand Mal Anfälle) (SCHWARTZ-PORSCHE 1984; LÖSCHER et al. 1985, LÖSCHER 1986; JAGGY und STEFFEN 1995 a und c). Die in der Literatur beschriebene Altersgrenze für das erste Auftreten von epileptischen Anfällen bei Hunden ist sehr weitläufig und liegt zwischen 6 Monaten bis hin zu 13 Jahren. Die meisten Autoren beschreiben jedoch, dass die ersten Anfälle bei Hunden mit idiopathischer Epilepsie meist zwischen dem 1. bis 3. Lebensjahr zu verzeichnen sind (BIELFELDT et al. 1971, OLIVER und LORENZ 1993, CHRISMAN 1991, SCHWARTZ-PORSCHE 1984 und FORRESTER et al. 1989, VANDEVELDE et al. 2001).

Im Hinblick auf die Entstehung epileptischer Anfälle sind in den letzten Jahren beträchtliche Fortschritte gemacht worden. Als Ursache der Epilepsien wird ein Ungleichgewicht zwischen den exzitatorischen und inhibitorischen Neurotransmittern vermutet (FENNER und HAAS 1989). Einem Verlust der GABAergen Inhibition (BURNHAM 1989; LÖSCHER 1989) steht die Hypothese eines initialen Überwiegens von Glutamat und der exzitatorischen Transmission (MCNAMARA 1988; DINGLEDINE et al. 1990) gegenüber. Weiterhin spielen bei der Epileptogenese veränderte Ionenkanäle und Störungen an den Neurotransmitter Rezeptoren eine wichtige Rolle (OWENS und KRIEGSTEIN 2001).

Hunde mit idiopathischer Epilepsie sind als Tiermodell für die Epilepsieforschung des Menschen gut geeignet (LÖSCHER et al. 1985 und LÖSCHER 1986), da bei beiden Spezies Pharmakosensibilität und Pharmakoresistenz bei der Anfallsbehandlung auftreten können. Ziel einer antiepileptischen Behandlung ist Anfallsfreiheit und möglichst wenig unerwünschte Nebenwirkungen während der Therapie. Beim Hund kann nur auf wenige Antiepileptika wie Phenobarbital, Primidon und

Kaliumbromid zugegriffen werden (SCHWARTZ-PORSCHE 1984, FREY und SCHWARTZ-PORSCHE 1985, FREY 1986, SCHWARTZ-PORSCHE und JÜRGENS 1991, LÖSCHER 1994).
Neuere antiepileptische Wirkstoffe, die bereits in die Humanmedizin Einzug gefunden haben, finden beim Hund keine Anwendung aufgrund zu kurzer Eliminationshalbwertszeiten und zu geringer therapeutischer Plasmakonzentrationen (LÖSCHER 1994).

Mit den derzeit zur Verfügung stehenden Antiepileptika werden oft nicht zufriedenstellende Behandlungserfolge erzielt. Etwa ein Drittel der Tiere wird anfallsfrei, ein weiteres Drittel zeigt eine deutliche Reduktion der Anfallsfrequenz und –intensität und bei dem verbleibenden Drittel kann medikamentös keine Besserung der Anfallsfrequenz und/oder der Intensität verzeichnet werden. Diese Hunde gelten als therapie- oder pharmakoresistent (SCHWARTZ-PORSCHE et al. 1982, FREY und SCHWARTZ-PORSCHE 1985, LÖSCHER et al. 1985, LÖSCHER und SCHWARTZ-PORSCHE 1986, HEYNOLD et al. 1997). Zusätzlich werden Nebenwirkungen beobachtet, die meist dosisabhängig auftreten (SCHWARTZ-PORSCHE et al. 1981, 1982 und 1985, SCHWARTZ-PORSCHE 1984, FREY 1989, PODELL 1996, LÖSCHER 1995). Zu diesen gehören ein erhöhtes Schlafbedürfnis, Gangstörungen, Schwäche, Polyphagie, Polydypsie und Polyurie (SCHWARTZ-PORSCHE et al. 1981, 1982 und 1985, BUNCH et al. 1982 und LÖSCHER 1995).
Unter der Therapie wird zudem häufig ein Ansteigen von Leberenzymen beobachtet (SCHWARTZ PORSCHE et al. 1985, LÖSCHER 1995).
Es besteht daher ein dringender Bedarf nach neuen, besser wirksamen und verträglicheren Antiepileptika für den Hund.

Basierend auf den Ergebnissen einer vorklinischen, experimentellen Studie von LÖSCHER und POTSCHKA (nicht publizierte Daten, 1998 a und b), bei der sich eine potente antiepileptische Wirkung und eine für den Hund

günstige Pharmakokinetik bestätigte, wurde in vorliegender Arbeit eine neue Substanz AWD 131-138 an Hunden mit idiopathischer Epilepsie überprüft.

In dieser Pilotstudie wurde an insgesamt 29 Hunden, die in der Klinik für kleine Haustiere der Tierärztlichen Hochschule Hannover wegen spontan auftretender Krampfanfälle vorgestellt worden waren, die neue antiepileptische Substanz AWD 131-138 getestet. Das Projekt war für einen Zeitraum von bis zu 9 Monaten geplant und wurde unter der Nummer 509c-42502-00A19 bewilligt.

Alle Hunde, die an der Studie teilnahmen, erfüllten folgende Einschlusskriterien: vor Behandlung mit AWD 131-138 hatten sie mindestens zwei oder mehr epileptische Anfälle. Bei der klinischen Allgemeinuntersuchung und der neurologischen Untersuchung fielen keine besonderen Befunde auf. Eine ausgedehnte Blutuntersuchung (Blutbild inkl. Differentialblutbild und blutchemische Analysen), sowie weitere Untersuchungen (Computertomographie des Schädels, Liquor cerebrospinalis) waren normal. Im Rahmen dieser Ausschlussdiagnostik wurde der Verdacht einer idiopathischen Epilepsie gestellt. Bei Hunden, die bereits mit einem Antiepileptikum behandelt wurden, musste die gemessene Serumkonzentration im therapeutischen Bereich liegen. Bei 12 Hunden wurde die idiopathische Epilepsie neu diagnostiziert, 17 Hunde hatten eine chronische Epilepsie und wurden entweder mit Phenobarbital oder Primidon vorbehandelt. Bei diesen Tieren erfolgte die AWD 131-138 Therapie als Kombinationstherapie. Allen 29 Besitzern wurde ein Fragebogen zugesandt. In diesem sollten Auskünfte über das Anfallsgeschehen vor und nach der Substanzgabe sowie eventuell auftretende Nebenwirkungen dokumentiert werden.

Die Messung der AWD 131-138-Konzentration im Plasma erfolgte durch die Firma, VIATRIS GmbH & CoKG, Frankfurt am Main (KNEBEL u. DONATH, unveröffentlichte Daten 1998). Für die Substanz AWD 131-138 lag die niedrigste zu messende Quantifikationsgrenze bei 0.5 ng/mL und das Detektionslimit bei 0.2 ng/mL. Diese Messungen wurden durchgeführt, um die Pharmakokinetik der Substanz bei an idiopathischer Epilepsie erkrankten Hunden nach einmaliger oraler Applikation und um die Compliance der Besitzer während des Studienverlaufs zu überprüfen. Die Dosierung von AWD 131-138 schwankte je nach Ansprechen auf die Therapie zwischen 20 und 60 mg/kg Körpergewicht und Tag.

Als Kontrollgruppe wurden 82 Hunde, die in der Zeit von Dezember 1999 bis Juni 2001 an der Tierärztlichen Hochschule Hannover untersucht wurden und an idiopathischer Epilepsie erkrankt waren, retrospektiv evaluiert. Bei diesen Hunden wurden die konventionellen Antiepileptika Phenobarbital, Primidon und Kaliumbromid eingesetzt.

Grosse Hunderassen waren in dieser Studie überrepräsentiert, Anfallstyp, Anfallsfrequenz und die Intensität der epileptischen Anfälle waren bei den einzelnen Hunden unterschiedlich.

Die Reduktion der Anfallsfrequenz bei Hunden, die nur mit der neuen Substanz AWD 131-138 behandelt worden waren, war vergleichbar mit den Hunden, die eine Therapie mit den konventionellen Antiepileptika Phenobarbital oder Primidon erhalten hatten. Es konnte keine statistische Signifikanz zwischen den einzelnen Behandlungsgruppen gesehen werden. Die Reduktion der Anfallsfrequenz bei Hunden, die mit Phenobarbital oder Primidon therapiert wurden, entsprachen zusätzlich Studienergebnissen wie sie von SCHWARTZ-PORSCHE et al. (1985) beschrieben wurden. Bei Hunden, die auf die Monotherapie mit Phenobarbital oder Primidon nicht ansprachen, wurde eine zusätzliche Gabe von AWD 131-138 oder

Kaliumbromid verabreicht. Durch dieses zweite Antiepileptikum konnte in beiden Gruppen eine Reduktion der Anfallshäufigkeit bei einigen Hunden beobachtet werden.

Die Anfallsdauer und die Schwere der Anfälle vor und während der Therapie wurden ebenfalls ausgewertet. Die Dauer des Iktus während eines Grand Mal Anfalls war in mehr als einem Drittel der Patienten, die mit AWD 131-138 behandelt wurden, verkürzt. Bei mit Phenobarbital therapierten Hunden wurde dieses Phänomen nur bei 1/10 der Hunde beobachtet, der Median der Iktusdauer war in dieser Gruppe sogar erhöht, der Iktus somit teilweise verlängert. Bei allen Therapiegruppen wurde beobachtet, dass die postiktale Phase während der Therapie kürzer war. Zusätzlich zu dieser Anfallsverkürzung wurde bei einigen Hunden beobachtet, daß während der AWD 131-138 Behandlung die Intensität einzelner epileptischer Anfälle schwächer war bzw. daß fokale Anfälle zugunsten von Grand Mal Anfällen auftraten. Bei Anfallsserien konnte eine Reduktion an Einzelanfällen gesehen werden. Viele Besitzer beschrieben zudem eine subjektive Besserung der Anfallsintensität.

Eine positive Wirkung der Substanz AWD 131-138 fiel bei Betrachtung der Nebenwirkungen wie Polyphagie, Polydipsie, Müdigkeit und Gangabnormalitäten auf. Bei der Therapie mit AWD 131-138 wurden im Vergleich zu den etablierten Antiepileptika wesentlich weniger Nebenwirkungen beobachtet. Die Compliance der Besitzer war bei den mit AWD 131-138 behandelten Hunden als sehr gut zu bezeichnen, speziell weil zu Anfang und während der Therapie keine Sedation auftrat. Regelmässig durchgeführte Blutuntersuchungen waren bei Hunden mit AWD 131-138 Monotherapie normal, ein Ansteigen der Leberenzyme (ALT, AP, GLDH), wie es bei der chronischen Applikation von Phenobarbital oder Primidon beobachtet wird, konnte nicht nachgewiesen werden.

Zusammenfassend ist zu berichten, daß mit der neuen Substanz AWD 131-138 in der vorliegenden klinischen Pilotstudie eine gute antikonvulsive Wirkung bei Hunden mit idiopathischer Epilepsie festgestellt werden konnte, die äquipotent zur Wirkung von konventionellen Antiepileptika wie Phenobarbital oder Primidon ist. Bei der chronischen Behandlung wurde AWD 131-138 sehr gut toleriert und es wurden deutlich weniger unerwünschte Nebenwirkungen im Vergleich zu den etablierten Antiepileptika beobachtet. Folgestudien mit einer größeren Patientenzahlen müssten dies bestätigen.

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IX Appendices

IX.1 Tables

Table 11: Seizure frequency per month in 12 dogs with newly diagnosed idiopathic epilepsy before (-) and during the treatment with AWD 131-138 (monotherapy)

	seizure frequency/month																	
Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
A.1.	*1*	*0*	*0*	*2*	*0*	*1*	*0*	*2*	*0*	0	0	0	0	2	0	2	0	0
A.2.	*1*	*0*	*0*	*1*	*1*	*1*	*2*	*2*	*3*	1	0	4	1	0	1	0	0	1
A.3.	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*1*	0	1	1	0	0	0	0	0	1
A.4.	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	*2*	3	4	5	0	0	1	0	3	0
A.5.								*2*	*1*	1	1	2	1	2	2	0	2	0
A.6.							*1*	*0*	*4*	0	0	0	0	0	0	0	0	0
A.7.									*2*	0	0	0	1	1	0	1	1	1
A.8.	*1*	*2*	*3*	*1*	*2*	*4*	*3*	*3*	*5*	2	3							
A.9.			*1*	*3*	*1*	*4*	*3*	*4*	*8*	7	6	9	7					
A.10.									*6*	0	0	2	0	0	0	0	1	
A.11.	*1*	*0*	*3*	*1*	*1*	*0*	*1*	*0*	*1*	1	0	0	0	1	0	1		
A.12.							*3*	*1*	*3*	2	2	2	1	1	2	1	0	

Legend: number of seizures per month, observation time before (cursive numbers) and during the treatment with AWD 131-138, dogs with bold print number died or were euthanized

Table 12: Seizure frequency per month in 44 dogs with newly diagnosed idiopathic epilepsy before (-) and during the treatment with phenobarbital (monotherapy)

	seizure frequency/month																	
Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
B.1.								*1*	*1*	6								
B.2.					*1*	*0*	*0*	*1*	*2*	0	0	0	0					
B.3.							*2*	*1*	*3*	0	2	0	0	0	0	0	0	0
B.4.	*0*	*0*	*0*	*1*	*0*	*1*	*2*	*0*	*1*	0	0	0	1	0	0	1	0	0
B.5.									*2*	3	0	0	0					
B.6.	*0*	*0*	*1*	*1*	*0*	*0*	*1*	*0*	*1*	0	0	0						
B.7.								*1*	*2*	0	0	0	0					
B.8.		*1*	*0*	*0*	*0*	*1*	*0*	*0*	*1*	0	0	0	0	0				
B.9.									*4*	1	1	0	0	0				
B.10.								*2*	*4*	0	0	1	0	1				
B.11.							*1*	*2*	*0*	0	1	1						
B.12.						*1*	*2*	*2*	*3*	1	1	1	0	1	1	0	0	
B.13.	*2*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*2*	0	0	0						
B.14.					*3*	*0*	*0*	*1*	*6*	0	2	0	1	4				
B.15.							*2*	*1*	*1*	0	0	0	0	0	0	0		
B.16.							*1*	*2*	*2*	0	0	0	0					
B.17.								*3*	*5*	1	0	0	2	1	0	0	0	0
B.18	*1*	*0*	*1*	*0*	*0*	*0*	*1*	*0*	*5*	0	2	1	0	2	0			
B.19.			*1*	*2*	*1*	*2*	*2*	*1*	*2*	1	2	2	1	2	2	1	2	
B.20.					*1*	*0*	*0*	*2*	*1*	7	9							
B.21.					*1*	*1*	*2*	*2*	*2*	4								
B.22.									*2*	0	0	0	0	0	0	0	0	0
B.23.									*4*	0	1	0						
B.24.			*1*	*2*	*1*	*3*	*2*	*5*	*7*	2	3	5						
B.25.	*1*	*0*	*0*	*1*	*0*	*0*	*2*	*1*	*2*	2	1	1	0	0	0	0	0	0
B.26.								*1*	*3*	2	0	1	0	2	0	1	0	2
B.27.				*2*	*2*	*1*	*2*	*1*	*3*	2	1	0	0	1	1	2	0	1

Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
B.28.					*2*	*0*	*2*	*0*	*0*	1	0	1	0	0	0	0	0	0
B.29.						*1*	*1*	*3*	*1*	0	1	0	2	0	0	1	0	1
B.30.								*2*	*2*	1	0	2	0	1	0	0	0	0
B.31.									*3*	2	10							
B.32.				*3*	*4*	*2*	*4*	*3*	*3*	0	0	1	0	0	0	3	4	2
B.33.	*3*	*0*	*0*	*0*	*0*	*0*	*0*	*7*	*6*	2	0	0	0	1	0	2	3	0
B.34.	*1*	*0*	*0*	*1*	*2*	*1*	*0*	*0*	*5*	1	0	0	0	1	0			
B.35.							*1*	*1*	*3*	0	0	0	0	0	0	0	0	0
B.36.	*0*	*1*	*0*	*2*	*1*	*3*	*0*	*2*	*1*	0	1	0	2	0	0	0	1	0
B.37.	*3*	*2*	*2*	*4*	*3*	*1*	*0*	*1*	*0*	0	0	2	1	0	0	0	1	0
B.38.							*1*	*3*	*4*	2	3	5	3	8				
B.39.				*4*	*4*	*3*	*2*	*4*	*3*	1	2	3	2	2	6			
B.40.						*1*	*4*	*0*	*1*	2	2	4						
B.41.								*1*	*2*	2								
B.42.									*2*	1	2	1	2	1	1	2	3	1
B.43.						*1*	*3*	*1*	*2*	1	3							
B.44.							*2*	*2*	*3*	3								

Legend: number of seizures per month, observation time before (cursive numbers) and during the treatment with phenobarbital, dogs with bold print number died or were euthanized

Table 13: Seizure frequency per month in 26 dogs with newly diagnosed idiopathic epilepsy before (-) and during the treatment with primidone (monotherapy)

	seizure frequency/month																		
Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
C.1.						*1*	*0*	*2*	*1*	0	0	0	0					
C.2.									*4*	4	3	1						
C.3.					*0*	*1*	*0*	*1*	*2*	0	0	1	0	0	1	0		
C.4.							*5*	*2*	*2*	0	0	0	2	1				
C.5.									*10*	12								
C.6.									*9*	0	0	0	0	0				
C.7.	*1*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*1*	0	0	0	0					
C.8.	*1*	*0*	*0*	*1*	*0*	*1*	*2*	*2*	*1*	0	0	1	0	1	0	0	1	0
C.9.	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*3*	0	0	0	0	0	0	1	0	0
C.10.					*1*	*0*	*1*	*2*	*2*	0	0	1	0	0	0	0	0	0
C.11.					*1*	*2*	*2*	*3*	*4*	2	0	1	2	0	1	0	1	0
C.12.	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*2*	0	0	0	0	1	0	0	1	1
C.13.								*3*	*4*	7	9							
C.14.	*0*	*0*	*3*	*0*	*0*	*2*	*0*	*0*	*2*	3	10							1
C.15.	*0*	*3*	*0*	*0*	*0*	*0*	*2*	*0*	*0*	4	10							
C.16.				*2*	*0*	*2*	*1*	*1*	*2*	0	0	1	0	0	0	1	0	0
C.17.	*1*	*1*	*1*	*1*	*0*	*2*	*1*	*1*	*1*	0	0	1	0	0	0	1	0	0
C.18.									*2*	0	0	0	0	0	0	0	0	0
C.19.				*1*	*3*	*4*	*2*	*0*	*2*	1	0	1	1	0	1	0	0	0
C.20.	*4*	*2*	*2*	*2*	*0*	*3*	*1*	*2*	*2*	0	0	0	0	0	0	1	0	0
C.21.	*1*	*2*	*3*	*3*	*1*	*3*	*2*	*2*	*2*	1	0	1	0	0	1	0	0	0
C.22.								*2*	*1*	1	3	8						
C.23.	*0*	*1*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	4	7							
C.24.									*4*	10								
C.25.									*4*	2	3							
C.26.							*5*	*8*	*7*	9	0	5						

Legend: number of seizures per month, observation time before (cursive numbers) and during the treatment with primidone, dogs with bold print number died or were euthanized

Table 14: Seizure frequency per month in 17 dogs with chronic epilepsy and add-on treatment with AWD 131-138

	seizure frequency/month																		
Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
D.1.	*2*	*3*	*0*	*0*	*1*	*4*	*0*	*5*	*1*	2	0	4	2					
D.2.	*2*	*0*	*1*	*2*	*1*	*2*	*2*	*1*	*2*	3	3							
D.3.	*2*	*2*	*4*	*1*	*4*	*2*	*4*	*1*	*5*	0	3	4						
D.4.	*4*	*3*	*3*	*2*	*3*	*3*	*4*	*2*	*3*	2	3	4	3	4	2			
D.5.	*2*	*3*	*2*	*0*	*1*	*4*	*3*	*0*	*2*	3	4	3	2	0	1	3	3	6
D.6.	*2*	*1*	*3*	*2*	*1*	*2*	*3*	*1*	*2*	3	2	2	1					
D.7.	*1*	*2*	*3*	*1*	*2*	*3*	*3*	*3*	*2*	0	3	0	4	2	2			
D.8.	*1*	*2*	*0*	*2*	*4*	*3*	*2*	*1*	*2*	0	4							
D.9.	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*2*	*4*	2	0	0	0	0	0	0	0	0
D.10.	*2*	*4*	*1*	*0*	*0*	*4*	*0*	*0*	*0*	0	0	0	0	2	0	0	0	0
D.11.	*1*	*2*	*1*	*2*	*0*	*2*	*1*	*1*	*2*	1	1	1	1	1	2	0	1	1
D.12	*4*	*3*	*1*	*3*	*4*	*5*	*3*	*3*	*2*	0	1	6	3	3	3	2	1	
D.13.							*2*	*2*	*4*	0	2	1	1					
D.14.							*1*	*3*	*2*	1	3	3	6	9	3			
D.15.			*2*	*1*	*1*	*2*	*1*	*2*	*4*	0	0	0						
D.16.		*3*	*1*	*2*	*2*	*2*	*2*	*5*	*3*	2	3	1						
D.17.			*3*	*4*	*2*	*4*	*3*	*3*	*6*	1	3	0	2	2	0	1	0	0

Legend: number of seizures per month with phenobarbital or primidone therapy (cursive numbers) and during the add-on treatment with AWD 131-138, dogs with bold print number died or were euthanized

Table 15: Seizure frequency per month in 12 dogs with chronic epilepsy with add-on treatment with potassium bromide

	seizure frequency/month																	
Dog	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
E.1.	*3*	*3*	*4*	*2*	*4*	*2*	*3*	*3*	*5*	3	2	0	1	2	0	1	1	1
E.2.	*1*	*2*	*5*	*1*	*2*	*1*	*1*	*2*	*2*	1	2	0	0	0	1	0	2	0
E.3.	*2*	*5*	*3*	*3*	*2*	*3*	*2*	*3*	*8*	3	2	0	0	0	0	0	0	0
E.4.				*8*	*5*	*6*	*3*	*5*	*4*	3	1	2	3	5	1	2	4	8
E.5.									*2*	3	0	0	0					
E.6.		*4*	*3*	*1*	*4*	*4*	*3*	*2*	*3*	1	3	2	1	0	0	0	0	0
E.7.	*2*	*1*	*2*	*1*	*2*	*2*	*2*	*1*	*2*	1	0	2	1	2	0	1		
E.8.				*1*	*0*	*2*	*5*	*8*	*13*	10	8	5	8	11				
E.9.	*1*	*2*	*3*	*5*	*4*	*5*	*6*	*3*	*4*	4	3	4	6	4	3	5		
E.10.	*2*	*3*	*1*	*2*	*2*	*6*	*3*	*3*	*5*	1	3	5	3	2	4	4	2	5
E.11.						*3*	*1*	*2*	*2*	2	3	3	5	4	2	5		
E.12.				*2*	*4*	*0*	*1*	*3*	*3*	2	3	2	4	2	3			

Legend: number of seizures per month with phenobarbital or primidone therapy (cursive numbers) and during the add-on treatment with potassium bromide, dogs with bold print number died or were euthanized

Table 16: 12 dogs with newly diagnosed epilepsy and AWD 131-138 monotherapy, breed, sex, bodyweight, age, age of first seizuring and AWD 131-138 daily-dosage (mg/kg bodyweight)

dog	breed	sex	body-weight (kg)	age (year)	age of first seizuring (years)	AWD 131-138 daily-dosage (mg/kg bodyweight)
A.1.	English Cocker Spaniel	m	14	5,5	2	40
A.2.	American Cocker Spaniel	f	11	5	2	30
A.3.	Newfoundland	m	55	4,5	2,5	30
A.4.	German Shepherd	m	36	5,5	4	50
A.5.	German Shepherd	m	62	4,25	4	30
A.6.	mixed breed	m	11	13	12,75	20
A.7.	Irish Setter	m	33	7,25	7	40
A.8.	Golden Retriever	m	36	4,5	2	40
A.9.	mixed breed	f	16	5	4,75	60
A.10.	German-Shorthaired	f	27	3,75	3,5	50
A.11.	German Shepherd	m	36	2,5	1,5	40
A.12.	mixed breed	nf	26	6,5	6,25	60

Legend: f= female, m= male, nf= neutered/female, dogs with bold print number died or were euthanized

Table 17: 44 dogs with newly diagnosed idiopathic epilepsy treated with phenobarbital monotherapy, breed, sex, bodyweight, age, age of first seizuring and phenobarbital daily-dosage

dog	breed	sex	body-weight (kg)	age (year)	age of first seizuring (years)	pheno-barbital daily/dosage (mg/kg bodyweight)
B.1.	Belgian Shepherd	f	32	4	3	4
B.2.	German Shepherd	f	26	4,75	3	6
B.3.	West-Highland-White-Terrier	f	8	13	12	4
B.4.	Dachshound	m	7,5	9	7,5	6
B.5.	Collie	f	14	0,75	0,5	4
B.6.	Harzer Fuchs	m	27	8,5	5	4,5
B.7.	Jack-Russell-Terrier	m	8,5	4,75	4	4
B.8.	Labrador Retriever	nf	23,5	3,25	2,5	6
B.9.	mixed breed	nm	32	2,25	2	6,4
B.10.	mixed breed	f	4	1	0,75	4
B.11.	Cocker Spaniel	m	15,5	7,5	6	6
B.12.	mixed breed	m	36	4,75	4,5	5
B.13.	mixed breed	f	16	2,25	1,75	4,8
B.14.	mixed breed	f	14	4,5	3,25	4
B.15.	Collie	m	25	4,75	3,5	6
B.16.	mixed breed	nm	33	1,25	1	4
B.17.	mixed breed	nf	40	2,75	1,5	5
B.18.	Miniature Schnauzer	m	9	4	2,5	4
B.19.	Belgian Malinois	nm	36,5	4,5	3,5	10
B.20.	German Shepherd	nf	41	1,5	1	4
B.21.	Border Collie	nm	24	1,5	1	13
B.22.	Beagle	m	12,5	2,75	2	4
B.23.	mixed breed	f	19	12,75	10	4
B.24.	Border Collie	f	23,5	1,25	1	11
B.25.	Dachshound	f	7,5	9,75	6	4

dog	breed	sex	body-weight (kg)	age (year)	age of first seizuring (years)	pheno-barbital daily/dosage (mg/kg bodyweight)
B.26.	Dalmatian	m	23,5	3,25	2,5	6
B.27.	Alaska Malamute	m	26	9,5	8	5
B.28.	Rhodesian Ridgeback	m	30	0,75	0,5	10
B.29.	Labrador Retriever	nm	38	3,25	2,5	10,5
B.30.	Samojede	m	32	4,75	3	8
B.31.	mixed breed	nm	34	3,25	2,5	6
B.32.	Labrador Retriever	m	37,5	3,25	2,5	8
B.33.	Golden Retriever	f	33,5	2,75	2,25	6
B.34.	Sheltie	f	9,5	3,75	2,5	4
B.35.	Papillon	f	6	2,5	2	4
B.36.	Labrador Retriever	nm	38,5	3,5	3	5
B.37.	Irish Setter	nf	35	3,25	2	4
B.38.	mixed breed	f	28	4	2,5	4
B.39.	Tibet Terrier	f	13	2	1,25	10
B.40.	Golden Retriever	nm	36,5	8	5,5	4,5
B.41.	German Shepherd	m	41	1,75	1,5	4,8
B.42.	Rottweiler	m	51	6,75	5,5	6
B.43.	Irish Setter	m	28	1,75	1,25	10
B.44.	Newfoundland	f	52	1,75	1,25	4

Legend: f= female, m= male, nf= neutered/female, nm= neutered/male, dogs with bold print number died or were euthanized

Table 18: 26 dogs with newly diagnosed idiopathic epilepsy treated with primidone monotherapy, breed, sex, bodyweight, age, age of first seizuring and primidone daily-dosage (mg/kg bodyweight)

dog	breed	sex	body-weight (kg)	age (year)	age of first seizuring (years)	primidone daily-dosage mg/kg bodyweight
C.1.	Brandelbracke	nf	24	5,5	5	70
C.2.	Saint Bernhard	nf	64,5	5,75	4,5	60
C.3.	mixed breed	f	28	3,5	2,5	70
C.4.	Collie	m	21	3,25	3	60
C.5.	German Shorthaired	m	28,5	8	7	60
C.6.	Weimaraner	nf	32	4,75	2,5	60
C.7.	West–Highland–White–Terrier	m	8	4,25	3	40
C.8.	Rhodesian Ridgeback	nf	31	3	1,5	40
C.9.	Labrador	f	30	4,5	3	60
C.10.	mixed breed	m	33,5	2,5	1,5	60
C.11.	Giant Poodle	nm	31,5	5,5	4,5	40
C.12.	mixed breed	m	7	6	4,5	60
C.13.	Boxer	nf	32,5	8,5	6	40
C.14.	Irish Setter	f	26,5	2	1	40
C.15.	Golden Retriever	nm	29	1,75	1	44
C.16.	Dachshound	m	5	4,5	2,25	30
C.17.	mixed breed	m	16,5	2,5	1	24
C.18.	Saint Bernhard	m	70	4,5	4	50
C.19.	mixed breed	f	31	1,5	1	50
C.20.	mixed breed	f	22	2,75	1,5	60
C.21.	Dachshound	m	7,5	3	2	30
C.22.	Dobermann	nm	34	7,75	7,5	60
C.23.	Weimaraner	m	32,5	1	0,75	30
C.24.	mixed breed	nm	41,5	2,75	2,5	60
C.25.	German Wirehaired	m	31	5,5	2,5	60
C.26.	mixed breed	nm	21,5	3,75	3	70

Legend: f= female, m= male, nf= neutered/female, nm= neutered/male, dogs with bold print number died or were euthanized

Table 19: 17 dogs with chronic epilepsy, add-on treatment with AWD 131-138, breed, sex, bodyweight, age, age of first seizuring and AWD 131-138 daily-dosage (mg/kg)

dog	breed	sex	body-weight (kg)	age (year)	age of first seizuring (years)	AWD 131-138 daily-dosage mg/kg bodyweight
D.1.	mixed breed	m	15,5	5	3,5	40
D.2.	Jack–Russell-Terrier	nm	7,5	4,5	2	40
D.3.	Rottweiler	m	55	5	2	20
D.4.	Magyar Viszla	m	29	5,5	1,75	40
D.5.	mixed breed	f	23,5	1,5	1	40
D.6.	Boxer	m	34,5	5,5	0,5	40
D.7.	English Spaniel	m	27	3,75	2,75	40
D.8.	Miniature Poodle	nm	8	4,5	2	30
D.9.	West–Highland–White-Terrier	nm	10	6,5	4	20
D.10.	Golden Retriever	m	32	4,5	3,5	20
D.11.	German Shepherd	m	45	4,5	3	40
D.12.	mixed breed	m	60	4,5	1	40
D.13.	mixed breed	m	27,5	2,5	2,25	30
D.14.	Collie	f	26	1,25	1	40
D.15.	German Wirehaired	m	38	9,5	8,5	20
D.16.	Fox-Terrier	m	11	3,75	3	40
D.17.	German Shepherd	m	44	7	6,5	30

Legend: f= female, m= male, nm= neutered/male, dogs with bold print number died or were euthanized

Table 20: 12 dogs with chronic epilepsy and add-on treatment with potassium bromide breed, sex, bodyweight, age, age of first seizuring and potassium bromide daily-dosage (mg/kg bodyweight)

dog	breed	sex	body-weight (kg)	age (years)	age of first seizuring (years)	potassium bromide daily-dosage mg/kg bodyweight
E.1.	mixed breed	nm	40	2,25	1,75	40
E.2.	Rhodesian Ridgeback	nm	41,5	1,25	1	40
E.3.	Golden Retriever	m	36,5	1	0,75	40
E.4.	Siberian Husky	nf	23	2,25	1	40
E.5.	Australian Shepherd	f	19,5	1,25	0,75	40
E.6.	Pyrenean Shepherd	nm	51	5,25	4	40
E.7.	mixed breed	nm	29,5	2,75	2	40
E.8.	Yorkshire Terrier	nm	5,5	7,5	5	60
E.9.	mixed breed	nm	27,5	2,25	2	40
E.10.	German Shorthaired	nm	34,5	4,5	1	50
E.11.	Swiss Mountain Dog	f	44	3	2	40
E.12.	Boxer	m	39	2	1,5	40

Legend: f= female, m= male, nf= neutered/female, nm= neutered/male, dogs with bold print number died or were euthanized

IX.2 Forms

Form 1: Neurological examination modified after JAGGY and TIPOLD (1999)

NEUROLOGISCHE UNTERSUCHUNG

Klinik Nummer: .....
Besitzer: ..... Datum: .....
Rasse: .....Alter .....Geschlecht.....

1. Bewusstsein: normal / Apathie - Stupor - Koma_____

2. Verhalten: normal / abnormal _____

3. Krampfanfälle: fokal / generalisiert / Status epilepticus / Cluster _____

4. Haltung: normal / abnormal: Kopfschiefhaltung rechts – links; gestreckte Kopf-Halshaltung; Paraplegie, Tetraplegie _____

5. Gang: normal / abnormal: Tetraparese; Paraparese; generalisierte Ataxie; Ataxie Hinterextremität; vestibuläre Ataxie; Drangwandern; Dysmetrie; Hypermetrie; Hypometrie; Kreisbewegungen rechts / links _____

6. Gehirnnerven

links		***rechts***
_____	II Sehen	_____
_____	Drohreflex	_____
_____	Wattebausch	_____
_____	II + III Pupillen	_____
___	Stimulation linkes Auge	___
___	Stimulation rechtes Auge	__
_____	II Fundus	_____
_____	III, IV, VI Strabismus	__
_____	Nystagmus	_____
_____	V Sensibilität	_____
_____	V Kaumuskeln	_____
_____	V Kiefertonus	_____
_____	VII Facialis (Mimik)	_____
_____	V, VII Lidreflex	_____
_____	V, VII Kornealreflex	_____
_____	IX, X Schlucken	_____
_____	X Sensibilität (Ohr)	_____
_____	XI Halsmuskeln	_____
_____	XII Zunge	_____
_____	Otoskopie	_____
_____	Augenhintergrund	_____

7. Haltungs- und Stellreaktionen

links		***rechts***
	Hüpfen	
_____	vorne	_____
_____	hinten	_____
	Korrekturreaktion	
_____	vorne	_____
_____	hinten	_____
	Schubkarren	
_____	mit Visus	_____
_____	Halsextension	_____
	Tischkantenprobe	
_____	optisch	_____
_____	taktil	_____
	Hemiwalking	
_____	vorne	_____
_____	hinten	_____

Aufrichtung _____
Unterstützung _____
Nackenreaktion _____

8. Spinale Reflexe

Vordergliedmassen

links ***rechts***

Ext.carpi rad.

_____ C7 - Th1 _____

Flexor

_____ C6 - Th2 _____

_____ Pannikulus _____

Hintergliedmassen

links ***rechts***

Patellarreflex

_____ L2- L4 _____

Tibialis cran.

_____ L4 - L7 _____

Flexor

_____ L2 - S3 _____

Perineal (S1-S3) _____

Bulbourethral (S1-S3) _____

Vulvourethral (S1-S3) _____

gekreuzter Extensor-Flexorreflex ___

Massenreflex _____

Shiff-Sherrington _____

Beurteilung

- 2 abwesend
- 1 herabgesetzt
  0 normal
+ 1 gesteigert
+ 2 Klonus

9. Sensibilität

Hyperästhesie _____

Analgesiezone _____

Hypalgesie _____

Oberflächensensibilität _____

Tiefenschmerz vorne rechts _____ links___

Hinten rechts _____ links___

Form 2: Certification of Analysis of AWD 131-138 pills

Analysenzertifikat Certificate of Analysis		**Zertifikat-Nr.: 0008980D** Certificate No.
Präparat: AWD 131-138 Tabletten 300 (AR 01) Preparation		
Charge: VV 00/17 Batch	**Chargengröße:** 5,83 kg	**Herstelldatum:** 27.11.2000 Manufacturing Date
Verwendung: zur Herstellung klinischer Prüfpräparate Use		**Herkunft:** Origin

Prüfung Test	**Spezifikation** Specification	**Ergebnis** Result	**Bewertung** Valuation
Beschreibung:			
Allgemeine Merkmale:	Weiße Tabletten oblong, gewölbt, beidseitig eine Bruchkerbe	Weiße Tabletten oblong, gewölbt, beidseitig eine Bruchkerbe	entspricht
Pharmazeutische Parameter:			
Durchschnittsmasse	Sollmasse: 615,0 mg ±2% (602,7 bis 627,3 mg)	614,4 mg	entspricht
Gleichförmigkeit der Masse	Sollmasse: 615,0 mg Abweichung von der Durchschnittsmasse: Mind.: 18 von 20: ± 5% Höchstens 2 von 20: ±10%	Durchschnittsmasse: 614,4 mg min.: 607,8 mg entspr. – 1,1% max.:621,3 mg entspr. + 1,1%	entspricht
Zerfallszeit in Wasser	nicht mehr als 15 min	bis 9 min (6:23 – 9:10 min)	entspricht
Bruchfestigkeit	mindestens 25 N	62 N (60,0 – 66,7)	entspricht
Gleichförmigkeit des Gehaltes	10 von 10 Tabletten: 85 bis 115% des Durchschnittsgehaltes	Mittelwert von 10 Tabletten: 295,5 mg / Tablette Abweichung vom Durchschnittsgehalt (297,3 mg): min.: 289,8 mg entspr. -7,5 mg = 2,5% max.:299,3 mg entspr. +2,0 mg = 0,7%	entspricht
Wirkstofffreisetzung in Puffer pH 6,8/0,75% Dodecylsulfat-Natrium	≥ 80% nach 30 min	nach 30 min: 100,0% RSD: 0,4% (99,4 – 100,4%)	entspricht

Analysenzertifikat Certificate of Analysis	**Zertifikat-Nr.: 0008980D** Certificate No.

Prüfung Test	**Spezifikation** Specification	**Ergebnis** Result	**Bewertung** Valuation
Identität: AWD 131-138	positiv Relative Retentionszeit des Hauptpeaks im Chromatogramm der Untersuchungslösung im Verhältnis zum Peak von AWD 131-138 im Chromatogramm der Referenzlösung: 0,9 – 1,1	positiv rel. Rt = 1,0	entspricht
Reinheit: verwandte Substanzen	1-(4-Chlorphenyl)-hydantoin: ≤ 0,5% andere Einzelverunr.: ≤ 0,5% Summe aller Verunr.: ≤ 1,0%	1-(4-Chlorphenyl)-hydantoin: < LOQ andere Einzelverunr.: rel.RT= 0,9 0,04% Summe aller Verun.: 0,04% (LOQ = 0,02%)	entspricht entspricht entspricht
Mikrobielle Qualität	Ph. Eur., 5.1.4, Kat. 3 A - höchstens 10^3 aerob wachsende Bakterien/g - höchstens 10^2 Pilze/g - Abwesenheit von Escherichia coli in 1 g	5 KBE / g 5 KBE / g nicht nachweisbar QKMD Befund-Nr. 1206/00 Prüf-Nr. MR 671/00	
Gehalt: AWD 131-138	289,75 mg – 315,00 mg / Tablette, berechnet auf die Durchschnittsmasse (entsprechend 95 bis 105% des deklarierten Gehalts)	297,3 mg/Tablette, berechnet auf die Durchschnittsmasse, entsprechend 99,1% des deklarierten Gehalts	entspricht

Prüfvorschrift: A FA PV 0092/01

Spezifikation: A FA FS 0094/01

Herstellanweisung: FG HA 385/01

Bearbeiter: QKMD, FAP-Ba, St

Befund: entspricht der Spezifikation;
Result freigegeben zur Herstellung klinischer Prüfpräparate bis 31.05.2001

Datum/Unterschrift:.13.12.2000
Date Signature

Kontrolleiter für klin. Prüfpräparate

Form 3: Owner agreement for AWD 131-138 treatment

Klinik für Kleine Haustiere
der
Tierärztlichen Hochschule Hannover
Bischhofsholer Damm 15
30171 Hannover

Einwilligung

_____

(Name, Vorname und Anschrift des Patientenbesitzers)

Mein Hund leidet an Epilepsie.

Ich bin einverstanden, das Medikament AWD 131-138 in der vorgeschriebenen Dosierung zu applizieren.

Ich wurde aufgeklärt, dass sich das Medikament in der klinischen Entwicklung befindet und von ihm keine krankmachende Wirkung ausgeht.

Ich bekomme das Medikament ohne Bezahlung, verpflichte mich jedoch, einen Anfallskalender zu führen und in regelmäßigen Abständen (1. Blutuntersuchung nach 3 Wochen) meinen Hund vorzustellen.

Weitere Blutuntersuchungen erfolgen nach Rücksprache.

_____

(Unterschrift des Patientenbesitzers)

Form 4: Questionnaire for the pet owners of AWD 131-138 treated dogs

Ihre Adresse

Name:

Anschrift:

Klinik für kleine Haustiere der
Tierärztlichen Hochschule Hannover
z.Hd. Frau Prof. Dr. A. Tipold oder TA S. Rieck
Bischhofsholer Damm 15

30173 Hannover

Hannover im Februar 2001

Fragebogen zur AWD-Medikamentenstudie

(Bitte zutreffendes ankreuzen oder beschreiben):

1. Sind die Eltern des Hundes bekannt?
2. Wissen Sie ob Wurfgeschwister ebenfalls an Epilepsie erkrankt sind?
3. Wann haben Sie ihrem Hund erstmalig AWD gegeben?
4. Welche Dosierung geben Sie zur Zeit pro Gabe?
5. Zu welchen Uhrzeiten geben Sie das Medikament?
6. In welchem Alter haben Sie die ersten epileptischen Anfälle beobachtet?
7. In welchen zeitlichen Abständen hat der Hund **vor** der AWD-Gabe das Krampfgeschehen gezeigt?
   vereinzelt pro Jahr Anzahl:
   mehrfach pro Monat Anzahl:
   mehrfach pro Woche Anzahl:
   mehrfach pro Tag Anzahl:
8. Wie häufig treten die Anfälle jetzt **während** der AWD-Studie auf?
   vereinzelt pro Jahr Anzahl:
   mehrfach pro Monat Anzahl:
   mehrfach pro Woche Anzahl:
   mehrfach pro Tag Anzahl:

9. Wird der Hund noch mit einem Zusatzmedikament gegen die Anfälle behandelt? (wenn ja, mit welchem und in welcher Dosierung?)
   _____
10. Hat sich die Stärke der Anfälle mit AWD
    □ gebessert □ gleichgeblieben □ verschlechtert
11. Wie lange dauerte ein Einzelanfall **vor** der AWD-Gabe?
    Sec. Min. Std.
12. Wie lange dauert ein einzelner Anfall **jetzt** mit AWD?
    Sec. Min. Std.
13. Krampft der Hund einmalig oder zeigt er mehrere Anfälle kurz hintereinander?_____
14. Wann beobachten Sie die Anfälle (tagsüber oder nachts)? Zu welcher Uhrzeit vornehmlich?_____
15. Sind die Anfälle unterschiedlich stark ausgeprägt? □ ja □ nein

Die folgenden Fragen beziehen sich auf das Anfallgeschehen *vor* der AWD-Gabe

16. Wie sieht der Anfall aus bzw. wie verhält der Hund sich während des Anfalls? (Bitte zutreffendes ankreuzen und evtl. beschreiben)
    _____
    _____
    _____

a) Bemerken Sie ob der Hund einen Anfall bekommen wird? □ ja □ nein
b) Ist der Hund unruhig vor dem Anfall? □ ja □ nein
c) Führt der Hund Kaubewegungen durch? □ ja □ nein
d) Liegt der Hund auf der Seite? □ ja □ nein
e) Führt der Hund Ruderbewegungen mit den Beinen aus? □ ja □ nein
f) Ist der Hund am ganzen Körper steif (Streckkrämpfe)? □ ja □ nein
g) Ist der Hund ansprechbar? □ ja □ nein
h) Setzt der Hund Urin ab während des Anfalls? □ ja □ nein
i) Setzt der Hund während des Anfalls Kot ab? □ ja □ nein
j) Bellt der Hund untypisch während des Anfallgeschehens? □ ja □ nein

k) Sind nur einzelne Körperregionen vom Anfall betroffen? □ ja □ nein
(z.B. einzelne Beine; Kopfstrecken, Augenzucken, Leckanfälle, nach nicht vorhandenen Fliegen schnappen, zittern einzelner Muskelgruppen) wenn ja, welche _____
oder der gesamte Körper? □ ja □ nein

17. Wann treten die Anfälle vornehmlich auf?
□ nach dem Essen
□ nüchtern
□ nach dem Spaziergang
□ nach voraus gegangenem Erbrechen
□ nach Streßsituationen
□ nach vergessener Medikamentengabe
□ anderen Begebenheiten Welche?_____

18. Treten die Anfälle aus dem Schlaf oder der Ruhe heraus auf?
□ ja □ nein

Fragen beziehen sich auf das Verhalten *während* der AWD-Gabe

19. Erholt der Hund sich mit AWD schneller wieder nach einem Anfall?
□ ja □ nein
wenn ja, in welchem Zeitraum?_____

20. Schläft der Hund lange nach einem Anfall? □ ja □ nein

21. Hat der Hund einen schwankenden Gang nach dem Anfall?
□ ja □ nein

22. Führt der Hund zwanghafte Bewegungen aus? □ ja □ nein
(z.B. drängen an der Wand entlang oder in Ecken; laufen gegen Gegenstände, laufen im Kreis)
wenn ja welche?_____

23. Findet der Hund sich nach dem Anfall in seiner gewohnten Umgebung zurecht? □ ja □ nein

24. Hat der Hund noch lange nach dem Anfall ein gesteigertes Bewegungsbedürfnis und kommt nicht zur Ruhe? □ ja □ nein

25. Frißt der Hund sofort nach einem Anfall? □ ja □ nein

26. Trinkt der Hund sofort nach dem Anfall? □ ja □ nein

27. Wurden Veränderungen in der Umgebung/Fütterung vorgenommen?
□ ja □ nein

28. Treten unter der Medikation Bewegungsstörungen auf? □ ja □ nein
wenn ja, welche: z.B. erschwertes Aufstehen;- gehen, wankender; stolpernder; taumeliger Gang; Gangunsicherheit)_____

29. Hat sich das allgemeine Befinden des Tieres unter der AWD-Medikation verändert? □ ja □ nein
wenn ja, wie _____

a) Ist der Hund durch AWD ruhiger geworden? □ ja □ nein

b) Hat der Hund ein vermehrtes Schlafbedürfnis? □ ja □ nein

c) Ist der Hund lebhafter geworden? □ ja □ nein

d) Ist der Hund jetzt spielfreudiger als früher? □ ja □ nein

e) Hat der Hund vermehrten Appetit? □ ja □ nein
wenn ja, über welchen Zeitraum?_____

f) Hat der Hund zugenommen? □ ja □ nein

g) Hat der Hund vermehrten Durst? □ ja □ nein

h) Reagiert der Hund langsamer auf ein Kommando? □ ja □ nein

i) Ist der Hund Streß-; Lärm- oder Lichtempfindlich? □ ja □ nein

j) Verhält der Hund sich gegenüber anderen Hunden aggressiver?
□ ja □ nein

k) Verhält sich der Hund nach AWD-Gabe anders als vorher? □ ja □ nein
wenn ja, wie_____

l) Ist der Hund nach AWD-Gabe unruhiger? □ ja □ nein

m) Zeigt der Hund ruheloses Wandern nach AWD? □ ja □ nein

Platz für Ihre Fragen oder Anmerkungen

_____

_____

_____

_____

_____

_____

_____

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