

New Antiepileptic Drug Candidate

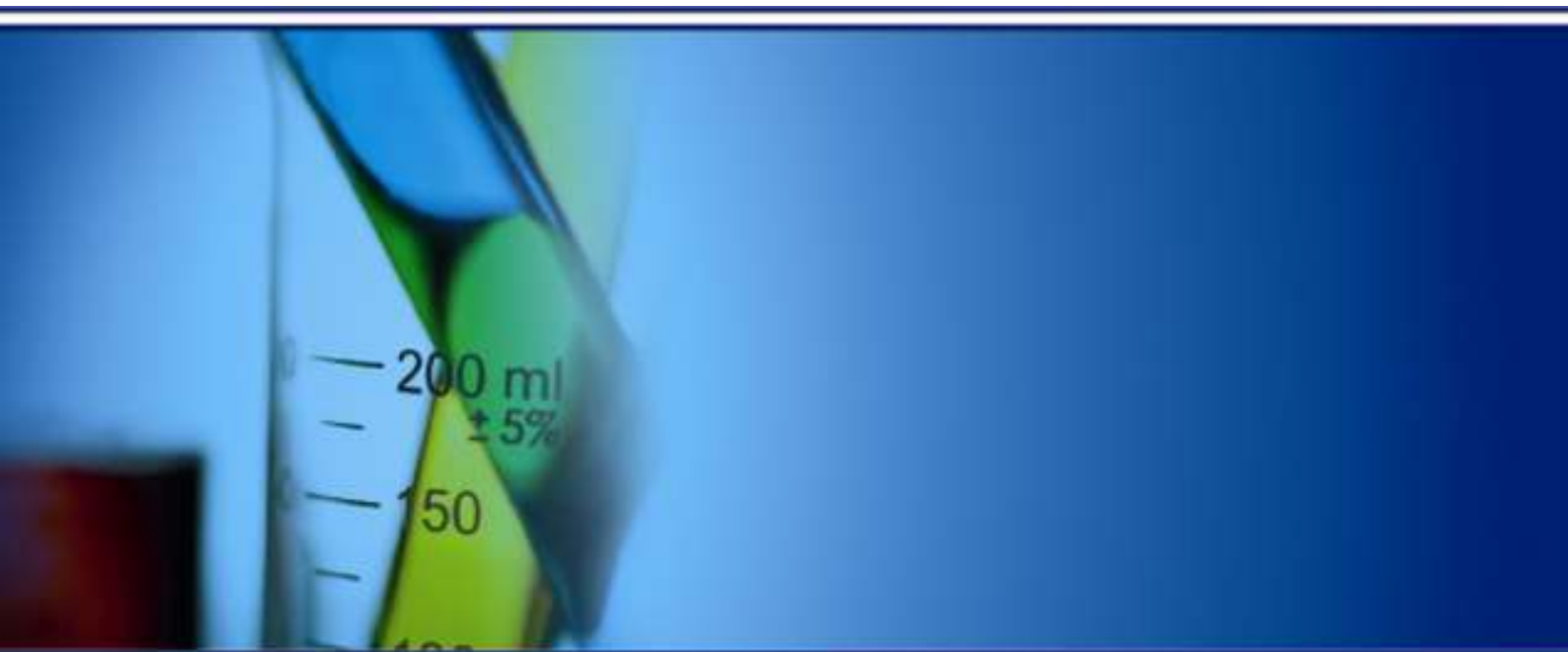


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1. Executive summary

We offer a focused drug development project for a novel antiepileptic drug which targets a steady niche market. Our brand new approach promises the treatment not only for the traditional epileptic cases but also the ~30% of epilepsy cases which are irresponsive to current antiepileptic therapy. The size of current antiepileptic drugs was more than 11.3 billion US dollars in 2008 (collective product sales). Therefore, the potential market of our novel compounds is huge.

The target is the pharmacological manipulation of gap junction channels that participate in non-synaptic intercellular communication, which is a novel therapeutic approach and have been extensively studied by our collaborative partner.

Our pending patent application covers 105 new type antiepileptic compounds. The lead molecules were examined *in vivo* and showed excellent antiepileptic effects. In a 28-day toxicity study no toxicity was observed.

2. Competitive advantage

Our new generation antiepileptic drug candidate is aimed to grant premium life quality for millions of patients.

Epilepsy cannot be cured yet but only controlled with currently marketed drugs – however, 30% of the seizures remain uncontrolled by current medication^{1,2}.

Based on emergent evidence it seems likely that our compounds could be proper candidates for targeted molecular therapy in order to develop new antiepileptic and anticonvulsant drugs that actually cure the disease.

3. Problem setting:

Epilepsy is a heterogeneous neurological disorder characterized by recurrent and spontaneous seizures. Despite progress in understanding the pathogenesis of experimental seizures and epilepsy, there are no available antiepileptogenic drugs that could prevent the development of epilepsy (epileptogenesis)^{3,4,5}. Therefore, medication is mostly directed at the suppression of ictogenesis (i.e. manifestation and spread of seizures in the already epileptic brain) by chronic administration of anticonvulsant drugs (also called as antiepileptic drugs (AEDs) in the literature). Nonetheless, seizures remain uncontrolled in at least 30% of all epilepsies by the currently available therapy^{1,2}. In general, these drugs act through by the modulation of voltage-gated ion channels, by enhancement of synaptic inhibition mediated by GABA_A receptors and by inhibition of synaptic excitation mediated by ionotropic glutamate receptors^{6,7,8}.

The search for possible new targets in combination with the use of new animal models considering the variations in the pathophysiological mechanisms that result in epilepsy may provide more successful strategies for the development of new drugs that might be effective also for the currently drug resistant epilepsies, as well as for preventing epileptogenesis.

The non-synaptic intercellular communication via gap junction (GJ) channels has been shown recently to be a novel synchronizing mechanism^{9,10,11,12} that contribute to the

manifestation and propagation of seizures and to the enhanced epileptogenicity of the adult and developing rat neocortex¹³.

Pharmacological manipulations of the GJ channels have been found to influence effectively the intensity of epileptiform activity. The blockade of these channels by a specific blocker, carbenoxolone^{14,15} exerted a strong anticonvulsive effect, whereas their opening with trimethylamine had a strong proconvulsive effect on the cortical seizure activity. In addition, molecular biological measurements revealed that epileptiform activity can upregulate the expression of some of the GJ channel forming proteins (connexins) mRNA levels after repeated seizures at both the primary focus and at the mirror focus¹³.

4. Market introduction

According to the World Health Organization, approximately 0.8% (50 million) of the world population suffers from epilepsy¹⁶. The above presented GJ approach fills in a market niche because it is bringing new opportunities for the patients.

Considering the fact that there are only 5 pending patents of 4 active ingredients (*carbamazepine, diazepam, lacosamide, oxcarbazepine, pregabalin, tiagabine hydrochloride*), and considering that the AED patents of Abbott and Glaxo has expired in 2009 we strongly believe that this new drug candidate will face substantial demand.

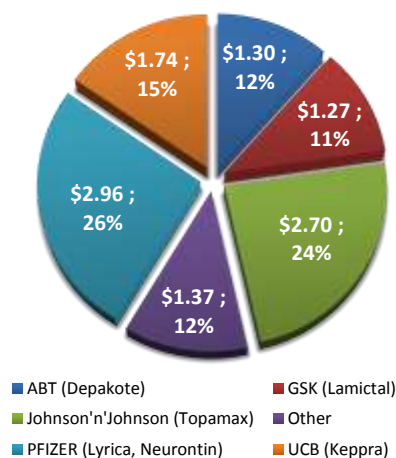
Product	Active Ingredient	Company	Patent Number	Publication Date	Estimated Expiry Date
Lyrica	pregabalin	Pfizer Inc	US 6197819	06.03.2001	30.12.2018
Trileptal	oxcarbazepine	Novartis AG	US 7037525	02.05.2006	12.08.2018
Vimpat	lacosamide	UCB S.A.	US RE38551	06.07.2004	17.03.2017
Vimpat	lacosamide	UCB S.A.	US 5654301	05.08.1997	05.08.2014
Diastat	diazepam	Valeant Pharmaceuticals International	US 5462740	31.10.1995	17.09.2013
Gabitril	tiagabine hydrochloride	Cephalon Inc	US 5010090	23.04.1991	30.09.2011
Carbatrol	carbamazepine	Shire plc	US 5326570	05.07.1994	23.07.2011
Tegretol XR	carbamazepine	Novartis AG	US 5284662	08.02.1994	08.02.2011
Topamax	topiramate	Ortho-McNeil Inc	US 4513006	23.04.1985	26.03.2009
Keppra	levetiracetam	UCB S.A.	US 4943639	24.07.1990	24.01.2009
Lamictal	lamotrigine	GlaxoSmithKline plc	US 4602017	22.06.1986	22.01.2009
Neurontin	gabapentin	Pfizer Inc	US 4894476	16.01.1990	02.11.2008
Depakote	divalproex sodium	Abbott Laboratories	US 4988731	29.01.1991	29.07.2008
Tegretol XR	carbamazepine	Novartis AG	US RE34990	04.07.1995	29.07.2007

1. AED patents (MedTrack)

The collective product sales of AED's were more than 11.3 billion US dollars in 2008¹⁷.

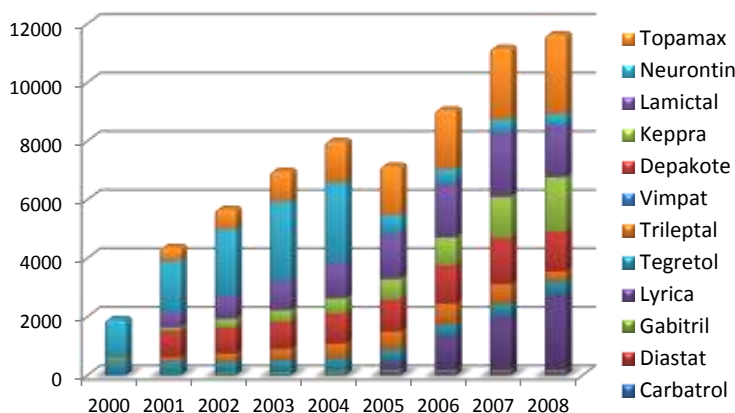
2008 Antiepileptics Market

(billion \$, % market share)



Product sales (worldwide)

(million \$)



2. AED sales and market shares (MedTrack)

5. Attractiveness:

Vichem performs advanced medicinal chemistry in the kinase inhibitory field based on its unique, in-house developed, Nested Chemical Library™ (NCL) technology. The NCL was designed on the platform of an up-to-date knowledge base we have built up from the knowledge accumulated in our more than 20 years of kinase inhibitory chemistry. Our library is organized around more than 110 core structures and more than 500 scaffolds, and contains inhibitors against more than 150 kinases. Utilizing our NCL, Masterkey, pharmacophore modeling and scaffold hopping technologies we can provide patentable lead compounds against selected kinases in five research cycles in about one year. Using our "Target Fishing"¹⁸ technology we can perform selectivity profiling and off-target identification. We can develop preclinical candidates with lead optimization for efficacy and ADMET in an additional 2 years. Vichem has lead compounds and/or early preclinical candidates for Tuberculosis, Influenza, AIDS and 5 pathological kinase targets. Vichem established partnership with various European, American and Japanese institutions and companies, participates in several FP7 projects.

6. Benchmark story

The media started to realize that this affliction has been overlooked. The 20.04.2009 Newsweek issue featured Epilepsy as the cover story - calling attention to the fact that up to 50.000 Americans die each year from seizures and related causes and there are more than 200.000 new cases each year and it is as common as breast cancer and takes as many lives.

7. IP issues

We have a pending patent application covering 105 new type antiepileptic compounds. Patent application number: P0900722.

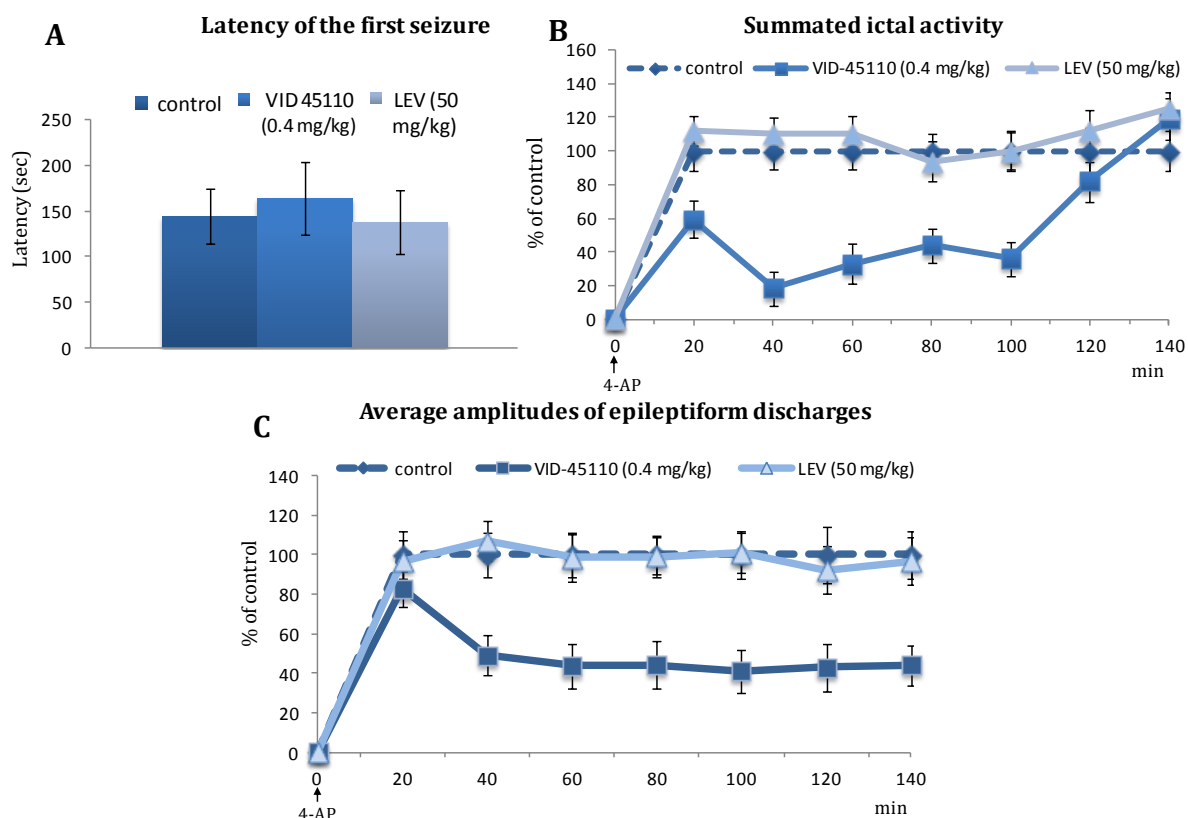
8. Results

The Nested Chemical Library™ was used for preselecting potentially antiepileptic compounds.

We searched for molecules, which anticonvulsive effects were comparable and competitive to that of carbenoxolone. For this reason we carried out experiments in which the tested molecules were applied together with the GJ blocker, carbenoxolone. Our results showed that anticonvulsive effects of one of the tested molecule, the VID-45110 and of carbenoxolone to some extent overlapped with one another. The anticonvulsive effect of VID-45110 was a bit more intensive, but had considerably longer duration than that of carbenoxolone. This finding suggests that VID-45110 may exert its effects at least partially through the blocking of the GJ channels.

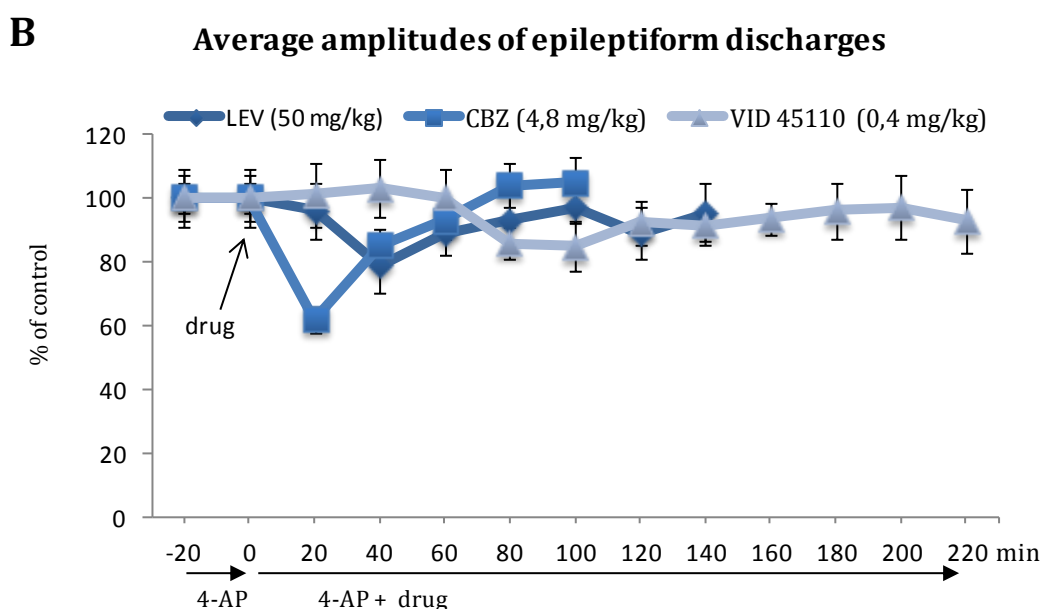
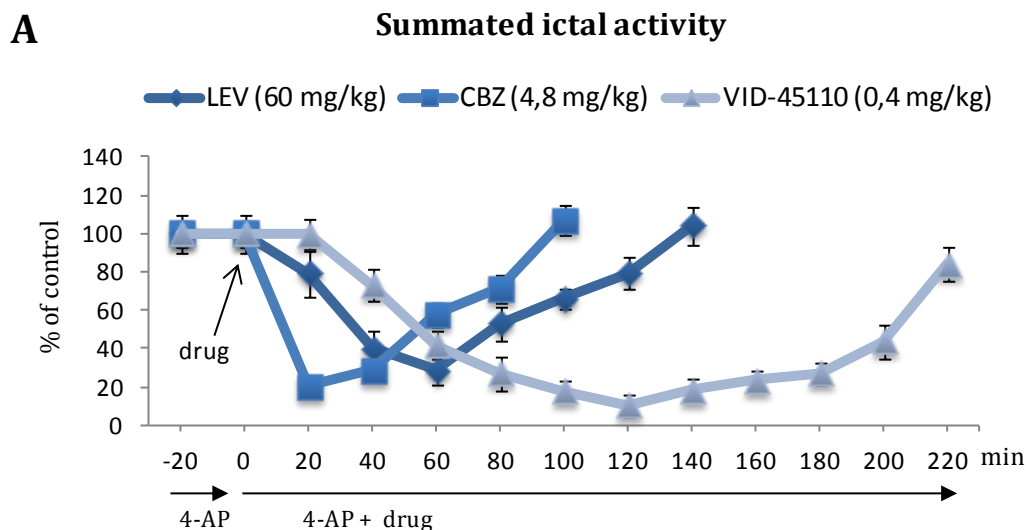
We tested the effects of some VID-45110 analog compounds on the induction, maintenance and propagation of seizure discharges on the 4-aminopyridine (4-AP)-induced *in vivo* epilepsy model, which provided good opportunities to investigate the periods of both epileptogenesis and ictogenesis. In order to estimate the power of the possible antiepileptogenic and/or anticonvulsant efficacy of these compounds we compared their data to the well-known and widely used AEDs (carbamazepin and levetiracetam) that were also tested on the 4-AP epilepsy model in identical circumstances. The results are shown in the following figures.

Antiepileptogenic effects of VID-45110 (preventive potential) after intravenous injection



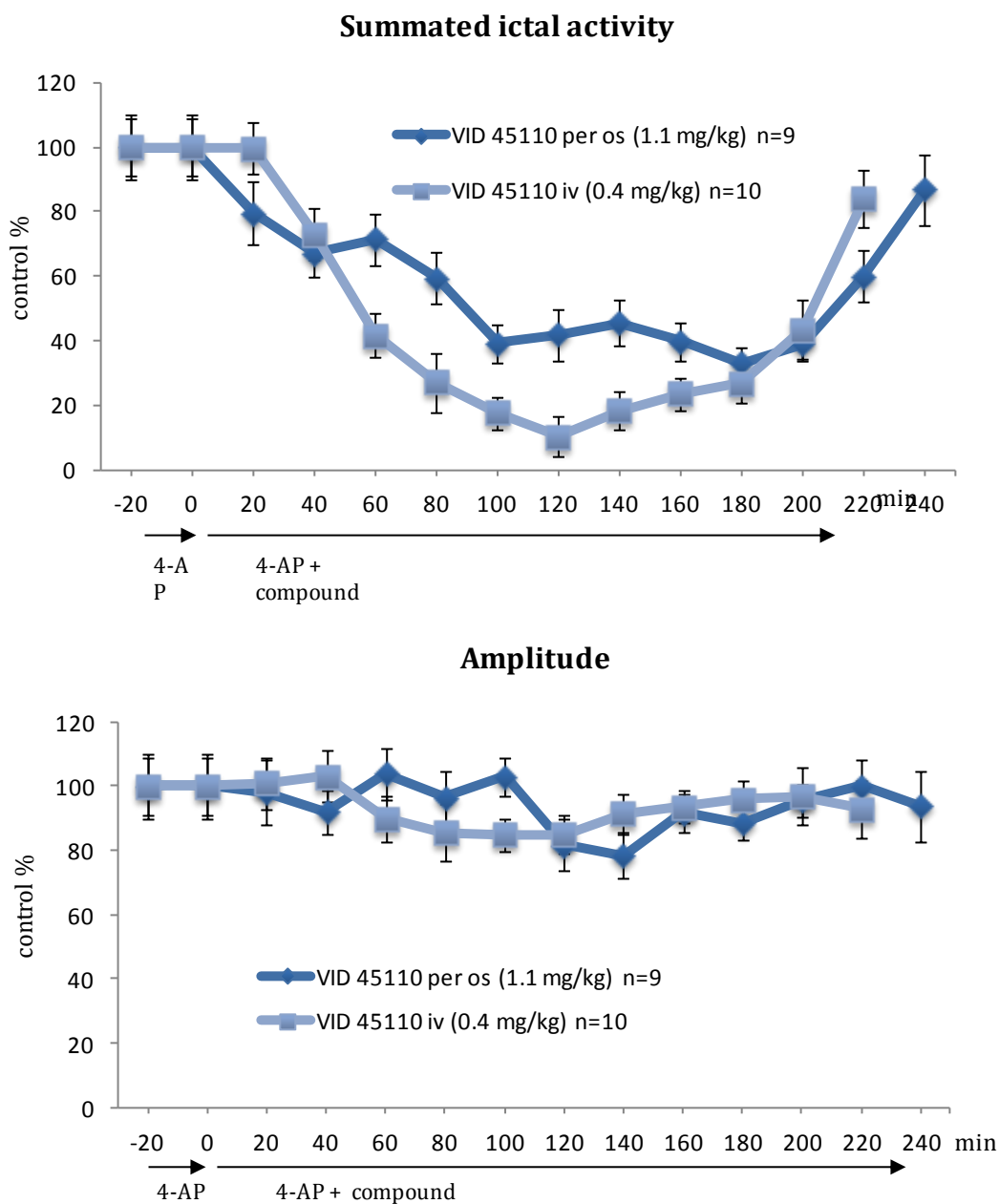
Effects of intravenous pretreatment of VID-45110 and of levetiracetam (LEV) on the latency of the first ictal period (**A**), on summated ictal activity (**B**) and on the average amplitude of seizure discharges (**C**) of cortical seizure activity induced by 4-AP (considered as control). Data are expressed as mean \pm SD. Stars indicate statistically significant changes. Significance criterion: $p < 0.05$.

Anticonvulsant effects of VID-45110 (decreasing epileptic seizures) after intravenous injection



Effects of intravenous application of VID-45110, levetiracetam (LEV) and carbamazepine (CBZ), respectively after 60 min of repeated seizures on the summated ictal activity **(A)** and on the average amplitudes of seizures discharges **(B)** of cortical seizure activity induced by 4-AP (considered as control). The ongoing treatment is indicated below each vertical arrow. -20 on the time scale represents the last 20 min of the preceding 60-min seizure activity induced by 4-AP (considered as control), just before the application of drugs. Data are expressed as mean \pm SD. Stars indicate significant changes. Significance criterion: $P < 0.05$.

Orally administrated vs. intravenous injection



No toxicity was observed in a 28-day toxicity study on 6 rats (3 female, 3 male). Examined parameters were mortality, external appearance, washing habit, motoric activity, eye and/or nose excretion, diarrhea, consciousness and mood.

9. Competitive environment

Antiepileptic therapy mainly consists of 12 drugs and the market size is almost 12 billion US dollars. The major competitors are listed in the table in the 'Market introduction' section. Since these drugs are effective in only 70% of cases and our compounds may be helpful to the remaining 30% of patients, our compounds will likely fill in a market niche.

10. Development plan

The *in vivo* test of the lead molecules and a 28-day toxicity study have been carried out with promising results. This will be followed by drug-likeness optimization and further development according to the following list:

- ADME/TOX optimization (ongoing)
- Preclinical documentation
- Clinical development
- Drug licensing
- Market launch

11. Investment opportunity

We offer a risk sharing approach model for our investors. All IP rights will be transferred to a spin-off company and an initial 15% of shares will be available for sale. Milestones met will be associated with a share-option for the investors and founders can either be diluted or new investors attracted to finance the next steps of development (with increasing funds creating increasing value).

This model significantly reduces the risk on the investor side and also allows flexibility and gain preservation from the side of the inventors who would like to retain consensus votes up till the final stages of preclinical documentation. At the stages of clinical development, investment capital majority vote is accepted.

The detailed work plan, timeline, the schedule of milestones, the milestone payments and possible royalties will be specified by a special research contract. The project will be implemented by a project company established by the investor and Vichem. Every milestone payment guarantees a higher share of ownership for the investor. At the end of the process the project company will be fully owned by the investor. In case of successful clinical trials (financed by the investor) and market launch, Vichem shall receive royalty payments. Milestone based payments and royalties are subjects for negotiation.

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¹⁷ MedTrack database (<http://www.medtrack.com>, accessed 2009.12.20)

¹⁸ Sharma K, Weber C, Bairlein M, Greff Z, Kéri Gy, Cox J, Olsen JV, Daub H. Proteomics strategy for quantitative protein interaction profiling in cell extracts. *Nat. Meth.*, 2009, 6(10): 741.