Clinical evaluation of imidapril in congestive heart failure in dogs: results of the EFFIC study

OBJECTIVES: The clinical efficacy and safety of imidapril were evaluated in dogs that presented with mild to severe congestive heart failure (New York Heart Association stage II to IV) by comparing the success rate of imidapril with a positive control by a non-inferiority approach.

METHODS: This good, clinical practice compliant, multicentre study (EFFIC study) enrolled 142 client-owned dogs and was conducted in 20 locations in France, Belgium and Germany. Dogs of various breed, age and weight were included in the study. These dogs were randomised into two groups that were treated for 84 days with either the test product, imidapril, or the positive control, benazepril, and followed up in parallel over this period. Both treatments were administered at a dose of 0.25 mg/kg once a day with the possibility of doubling this dose to 0.5 mg/kg if considered necessary from a clinical point of view. In addition, concomitant treatment was given to dogs presenting with pulmonary oedema and/or ascites, supraventricular tachyarrhythmia and/or dilated cardiomyopathy. The evolution of the New York Heart Association stage and the “functional signs” score were evaluated as primary efficacy criteria.

RESULTS: The success rate in the imidapril group was 66 compared with 68 per cent in the benazepril group. Regarding safety, 35 dogs in each group experienced at least one adverse event. Nine dogs in each group experienced at least one serious adverse event. The difference between these results was not statistically significant.

CLINICAL SIGNIFICANCE: Imidapril is as efficacious and safe as the reference product, benazepril.

INTRODUCTION

The two most common causes of chronic congestive heart failure (CHF) in dogs are mitral valve disease (MVD) and dilated cardiomyopathy (DCM). These diseases are progressive and result in activation of neurohormonal compensation mechanisms to preserve appropriate cardiovascular function. There is convincing evidence that these mechanisms become noxious when they are chronically activated and that they play a significant role in the pathology of heart failure (Koch and others 1995, Pedersen and others 1995). Therefore, it is considered that the suppression of the renin-angiotensin-aldosterone system with an angiotensin-converting enzyme inhibitor (ACEI), when added to other medical therapies, improves the clinical signs and prolongs the life expectancy in human beings (CONSENSUS Trial Study Group 1987, SOLVD Investigators 1992) and dogs with CHF (COVE Study Group 1995, IMPROVE Study Group 1995, Ettinger and others 1998). Moreover, it was shown in previous studies on angiotensin-converting enzyme inhibition (ACEI) in naturally occurring heart disease in dogs that ACEI are efficacious in combination with other therapies. They are now widely used in the medical treatment of CHF in dogs (Kitagawa and others 1997, BENCH [BENazepril in Canine Heart Disease] Study Group 1999, Kolm and Kosztolich 1999).

The purpose of the EFFIC (Efficacy of Imidapril in Congestive heart failure) study was to compare the efficacy and safety of the ACEI imidapril with a reference product, benazepril, a well-established ACEI.

MATERIALS AND METHODS

Inclusion criteria

In this good clinical practice compliant field study, a total of 142 client-owned...
dogs were treated and followed up for 84 days in 20 veterinary practices located in France, Germany and Belgium.

All dogs included were in stage II to stage IV (according to the New York Heart Association [NYHA]) heart failure due to MVD or DCM. Echocardiography and thoracic radiography were carried out before inclusion in order to identify the cardiac disease causing the CHF. Non-inclusion criteria are summarised in Table 1.

**Study design**

Dogs were treated with either imidapril solution (containing 2.5 mg, 5 mg or 10 mg of imidapril per ml) (Prilium; Vetoquinol SA) or with benazepril tablets (containing 5 mg or 20 mg of benazepril per tablet) (Fortekor; Novartis) as the reference product. Both treatments were administered orally, once a day, at a dose of 0.25 mg/kg for 84 days. If required by the animal’s state of health, the clinician investigator was allowed to double the dose of imidapril or benazepril during the study, keeping the principle of a single daily dose.

All other ACEis, angiotensin II receptor antagonists, calcium antagonists, nitrates, derivatives, beta-blockers and pimobendan were not authorised during the study. Authorised concomitant treatment, in particular diuretics and digitalis drugs, were permitted for dogs presenting with pulmonary oedema and/or ascites, supraventricular tachyarrhythmia and/or DCM. No statistically significant difference was found between the two treatment groups regarding the frequency of use of concomitant treatments.

The study was conducted under blind conditions by the dual investigator method: the clinician investigator examining the dog was not aware of whether the dog was receiving benazepril or imidapril. Due to the different study drug formulations, the owners were able to know their dog’s treatment. However, they were advised not to inform the clinician investigator. An informed consent was obtained from all owners before the enrolment of their dogs in the study.

Dogs that had not received ACEis during the six weeks preceding inclusion were considered “naive dogs” whereas those that had been undergoing regular ACEi treatment for six weeks or longer before inclusion were called “pre-treated dogs”. They were therefore randomised separately.

The dogs were evaluated at the selection visit and at the follow-up visits performed on day 0, 14, 28 and 84. At the selection visit, a clinical examination and an echocardiographic and radiographic evaluation (thorax, at least a lateral view) were performed to confirm the heart condition. In addition, haematological and serum biochemical profiles were carried out to establish baseline values. At the follow-up visits, clinical examinations were performed; all data relating to efficacy were recorded as well as any adverse event. (AE) Additional serum biochemical profiles were also performed. In order to evaluate the efficacy of the heart failure therapy, various clinical parameters were selected and used by the clinician investigator to assess the condition of the dog at each visit.

The primary efficacy criterion “success rate” was defined as:

- the NYHA score on day 84 is inferior to the NYHA score on day 0 or
- the NYHA score on day 84 is equal to the NYHA score on day 0 and the functional signs score on day 84 is inferior to the functional signs score on day 0.

The functional signs score was the sum of the exercise tolerance, dyspnoea, frequency of cough and ascites clinical scores (Table 1).

### Table 1. Inclusion/non-inclusion criteria and scoring grid

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Non-Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs in stage II to stage IV heart failure (according to the NYHA) following MVD or DCM</td>
<td>Dogs with an estimated vital prognosis of less than six months because of a disease other than heart failure</td>
</tr>
<tr>
<td>Modified NYHA classification system for heart failure (Knight, 1995)</td>
<td>Dogs with a history of hypersensitivity to ACEi or of poor compliance with ACE treatment in the past or at inclusion</td>
</tr>
<tr>
<td>No statistically significant difference was found between the two treatment groups regarding the frequency of use of concomitant treatments.</td>
<td>Dogs that had already received treatment with an ACEi could be included unless this treatment had been implemented in the six weeks preceding inclusion. The current treatment had to be stopped on the inclusion day and replaced with the test product without any washout period</td>
</tr>
<tr>
<td>Dogs presenting with congenital heart disease diagnosed by medical imaging</td>
<td>Dogs with an estimated renal dysfunction and/or whose blood creatinine level was above 220 µg/ml at the day of inclusion</td>
</tr>
<tr>
<td>Breeding animals and gestating or lactating bitches for safety reasons</td>
<td>Dogs with a history of hypersensitivity to ACEi or of poor compliance with ACE treatment in the past or at inclusion</td>
</tr>
<tr>
<td>Dogs weighing less than 5 kg or more than 60 kg</td>
<td>Dogs with an estimated renal dysfunction and/or whose blood creatinine level was above 220 µg/ml at the day of inclusion</td>
</tr>
<tr>
<td>Dogs presenting with congenital heart disease diagnosed by medical imaging</td>
<td>Dogs with an estimated renal dysfunction and/or whose blood creatinine level was above 220 µg/ml at the day of inclusion</td>
</tr>
</tbody>
</table>
| NYHA New York Heart Association, MVD Mitral valve disease, DCM Dilated cardiomyopathy, ACEi Angiotensin-converting enzyme inhibitor, ACE Angiotensin-converting enzyme inhibitor

**Exercise tolerance**

- (0) None
- (1) Slight reduction
- (2) Severe reduction
- (3) Exercise impossible

**Frequency of cough**

- (0) None
- (1) Rare
- (2) Frequent
- (3) Permanent

**Dyspnoea**

- (0) None
- (1) On intense effort (e.g. running, climbing stairs)
- (2) On moderate effort (e.g. walking)
- (3) At rest

**Ascites**

- (0) None
- (1) Moderate
- (2) Severe

**Table 1. Inclusion/non-inclusion criteria and scoring grid**
The secondary criteria for assessing efficacy were the evolution of the other clinical scores from day 0 to day 84, such as general health, appetite, fatigue, syncope, dyspnoea, mucous membrane colour, heart rate, cardiac arrhythmia and pulmonary auscultation, and the survival rate on day 84. Finally, the clinician investigator and the owner were asked to provide an overall assessment of the treatment at the end of the dog’s follow-up period using an overall satisfaction score.

Tolerance was assessed at each visit by the clinician investigator who recorded any AE, more specifically the new signs associated with aggravation of heart failure. The safety assessment criteria were the frequency of AEs and the evolution of the serum biochemical parameters from the selection visit to day 84.

The owners observed their dogs after administration of each dose and completed a daily log verifying the drug administration and reporting their observations.

**Statistical methods**

Data from all the dogs included were combined and analysed to compare the imidapril and the benazepril groups. The calculation of the sample size was based on the following expectations (Donner 1984): an a priori equivalence limit of -20 per cent, an expected success rate for the reference group of 65 per cent and an expected success rate for the tested group close to the reference group. With a power of 80 per cent and a type I error of 5 per cent (one-sided test), a sample size of 140 animals was expected to be sufficient for the statistical analysis of the primary efficacy criterion.

Before the efficacy analysis, on day 0, the initial characteristics of the study population were compared. All analyses on initial characteristics were performed on the intention-to-treat (ITT) subsample, using two-sided tests. For qualitative variables (ordered or not), chi-squared test or Fisher’s exact test (for 2x2 tables, or if at least one expected count was less than 5) were used. Student’s t test or Wilcoxon’s test (in case of non-normal distribution) were applied on quantitative variables.

The efficacy analysis has been performed according to the ITT principle. Hence, all the randomised cases were analysed for the assessment of efficacy.

In addition, to enforce the explanatory power of the analysis of the primary efficacy criterion “success rate”, a “per-protocol” (PP) analysis has been conducted, excluding dogs for which a major deviation to the protocol occurred.

Since the objective of the study was to compare the new product with an active control, a non-inferiority approach, which was recommended dose), respectively. A log rank test was performed to compare treatment groups with respect to survival rate (when the follow-up of a dog was stopped because of protocol deviation, AE or death not attributable to the treatment, the value was censored).

Regarding tolerance, the difference in frequency of AEs between the two groups was tested using the Fisher’s exact test. To compare biochemical parameters from day 0 to day 84, a two-factor ANOVA (treatment, time and treatment-time interaction) with repeated measures was applied. All the statistical tests performed for the clinical parameters, overall assessments, survival and safety parameters were two-sided, with a level of type I error of 5 per cent.

### RESULTS

#### Initial characteristics of the study population

The two treatment groups were well balanced: 72 dogs in the benazepril group versus 70 in the imidapril group. As expected, more naive (102 dogs, 71.8 per cent) than pre-treated dogs (40 dogs, 28.2 per cent) were included. The demographic characteristics of the included dogs are presented in Table 2. The differences in the baseline were of no statistical significance between the two treatment groups.

All parameters relating to clinical signs, except cough frequency, were distributed with no statistical significance between the two treatment groups. Since cough frequency was taken into account for the determination of the stage of heart failure, and since there was no difference between the groups with respect to NYHA stage, the observed difference related to cough

| Table 2. Demographical characteristics of the treatment groups |
|-------------------|------------------|------------------|
|                   | Imidapril (n=70) | Benazepril (n=72) |
| Age (years)       | 10.9             | 10.7             |
| Mean              | 2.81             | 2.82             |
| Breed size        |                  |                  |
| Large             | 14 (20%)         | 9 (12.5%)        |
| Medium            | 16 (22.9%)       | 16 (22.2%)       |
| Small             | 40 (57.3%)       | 47 (65.3%)       |
| Sex               |                  |                  |
| Female            | 14 (20%)         | 15 (20.8%)       |
| Neutered male     | 5 (7.1%)         | 7 (9.7%)         |
| Spayed female     | 12 (17.1%)       | 13 (18.1%)       |
| Male              | 39 (55.7%)       | 37 (51.4%)       |
| Neutered female   | 7 (10.0%)        | 5 (6.2%)         |
| NYHA stage        |                  |                  |
| Class 1           | 0                | 0                |
| Class 2           | 38 (53.9%)       | 44 (61.2%)       |
| Class 3           | 27 (38.6%)       | 26 (36.1%)       |
| Class 4           | 5 (7.1%)         | 2 (2.8%)         |
| Nature of the heart disease |                  |                  |
| DCM               | 12 (17.1%)       | 9 (12.5%)        |
| MVD               | 51 (72.9%)       | 52 (73.2%)       |
| MVD+other         | 4 (5.7%)         | 3 (4.2%)         |
| DCM+MVD           | 3 (4.3%)         | 3 (4.2%)         |
| Other             | 0                | 5 (6.9%)         |
| ACE status        |                  |                  |
| Naive             | 50 (71.4%)       | 52 (72.2%)       |
| Pre-treated       | 20 (28.6%)       | 20 (27.8%)       |

NYHA New York Heart Association, DCM Dilated cardiomyopathy, MVD Mitral valve disease, ACE Angiotensin-converting enzyme.
frequency was not considered as having an impact on further study results.

**Study compliance**

Compliance with the treatment schedule was satisfactory. The mean administered dose was 96.1 per cent of the recommended dose in the imidapril group and 96.9 per cent of the recommended dose in the benazepril group, respectively.

During the study, the dose was doubled for 17.7 per cent (12 of 70) and 8.6 per cent (six of 72) of the dogs in the imidapril and benazepril groups, respectively. However, this difference between both treatment groups remained statistically not significant.

As described in section Statistical Methods, a PP analysis was conducted to enforce the explanatory power of the analysis performed according to the ITT principle. Hence, 10 cases were excluded from the PP subsample (five in each treatment group). Six dogs had received less than 80 per cent of the dosage foreseen in the protocol over the treatment period, three dogs did not satisfy the inclusion criteria (ACEi treatment initiated less than six weeks before inclusion) and one dog was prescribed pimobendan, which was a forbidden concomitant treatment.

**Success rates at the end of follow-up**

The evolution of the NYHA stage from day 0 to day 84 is presented in Fig 1 for each treatment group. The primary efficacy criterion “success rate” was 65.7 per cent (46 of 70 dogs) in the imidapril group and 68.1 per cent (49 of 72 dogs) in the benazepril group, respectively. The observed odds ratio was 0.90. The hypothesis of non-equivalence with an a priori equivalence limit of 0.90 per cent was rejected with \( P < 0.05 \). The ITT analysis demonstrated that the results were statistically not different in both treatment groups, which was confirmed by the PP analysis (Table 3).

In conclusion, both treatments gave satisfactory and equivalent results in terms of success rate at the end of the follow-up period.

The success rates, adjusted according to the treatment status of dogs at inclusion (naive versus pre-treated dogs), are detailed in Table 3. These adjusted “success rates” were 70.0 and 75.0 per cent in the naive group and 55.0 and 50.0 per cent for the pre-treated dogs, respectively. The results of the non-inferiority test were consistent with those of the primary overall analysis, which led to the conclusion that imidapril was not inferior to benazepril in terms of efficacy.

**Table 3. Distribution of dogs according to the “success rates” for each treatment group**

<table>
<thead>
<tr>
<th>Success rate</th>
<th>Imidapril</th>
<th>Benazepril</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat, overall (142 dogs)</td>
<td>Success</td>
<td>46/70 (65.7%)</td>
<td>49/72 (68.1%)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>24/70 (34.3%)</td>
<td>23/72 (31.9%)</td>
</tr>
<tr>
<td>Per-protocol, overall (132 dogs)</td>
<td>Success</td>
<td>42/65 (64.6%)</td>
<td>46/67 (68.7%)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>23/65 (35.4%)</td>
<td>21/67 (31.3%)</td>
</tr>
<tr>
<td>Intention-to-treat, stratified (stratification: status at inclusion) (142 dogs)</td>
<td>Status: naive</td>
<td>35/50 (70.0%)</td>
<td>39/52 (75.0%)</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>15/50 (30.0%)</td>
<td>13/52 (25.0%)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>11/20 (55.0%)</td>
<td>10/20 (50.0%)</td>
</tr>
<tr>
<td>Intention-to-treat, stratified (stratification: nature of the congestive heart failure) (142 dogs)</td>
<td>Status: MVD or other</td>
<td>36/55 (65.5%)</td>
<td>39/60 (65.0%)</td>
</tr>
<tr>
<td></td>
<td>Success</td>
<td>19/55 (34.5%)</td>
<td>21/60 (35.0%)</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>10/15 (66.7%)</td>
<td>10/12 (83.3%)</td>
</tr>
<tr>
<td></td>
<td>Status: DCM or DCM = MVD</td>
<td>5/15 (33.3%)</td>
<td>2/12 (16.7%)</td>
</tr>
</tbody>
</table>

n.s. Not significant, DCM Dilated cardiomyopathy, MVD Mitral valve disease
Other clinical parameters
The evolution of the clinical scores demonstrated that time had a statistically significant effect on all the assessed clinical parameters, except heart rate. The following clinical signs definitely showed an improvement between day 0 and day 84 in both groups: general health, fatigue at rest, effort tolerance, dyspnoea, frequency of cough, pulmonary auscultation and NYHA score. There was no statistically significant difference between the two treatment groups with regards to the evolution of the clinical parameters. This was consistent with the analysis of the primary efficacy criterion “success rate”.

Overall assessment
The overall efficacy was evaluated in a blind manner by the clinician investigators and by the owners. Their assessments are presented in Fig 3 and were not significantly different between groups (P = 0.63 and 0.30, respectively).

The survival curves are shown in Fig 2. Both curves show a parallel evolution over the follow-up duration. The survival rates at the end of the follow-up were 91.1% per cent in the imidapril group (six failures, 61 dogs completed the follow-up) and 88.7 per cent in the benazepril group (eight failures, 61 dogs completed the follow-up). Again, no statistically significant difference was demonstrated between treatment groups with respect to survival rate (log rank P = 0.63, n.s. [not significant]).

Treatment safety
The safety assessment criteria were the frequency of AEs and the evolution of the serum biochemical parameters from the selection visit to day 84. An AE was defined as any undesired event, expected or not, suffered by a dog taking part in the study, whether or not this event was regarded as attributable to the tested product. Fifty and 48 per cent of the dogs (35 dogs in each group) experienced at least one AE over their follow-up in the imidapril and benazepril groups, respectively. Nine dogs in each group experienced at least one serious AE. There was no statistically significant difference between the treatment groups concerning this distribution of dogs according to the occurrence of at least one AE (P > 0.99, n.s.).

For 32 of the AEs, the investigator could not exclude a relationship with the treatment, 18 in the imidapril and 14 in the benazepril group, respectively. Among these were four serious AEs. One dog from the benazepril group died. The cause of death was considered to be cardiac in origin. Another member of this group underwent icterus from day 64 onwards. Eventually, euthanasia was performed on day 84 as the dog was dying. One dog from the imidapril group died due to worsening of CHF, and another one died at the owner’s premises on day 27, probably also due to cardiac failure. Causality for the second dog was assessed as “possible” by the investigator, although the information about the dog’s death was given only by the owner.

No specific tolerance issue was raised by the analysis of the evolution of the biochemical results in both treatment groups.

DISCUSSION
The objective of the EFFIC study was to compare the efficacy and safety of two ACEis, imidapril and benazepril, for treating mild to severe CHF in dogs affected by spontaneous MVD or DCM. This good, clinical practice compliant, multicentre study demonstrates that imidapril is as efficacious and safe as the reference product, benazepril.

This study aimed at simulating the use of products in field conditions in daily practice, thus only clinical endpoints and common diagnosis methods were used for their evaluation and selection. Moreover, heart failure is a clinical syndrome, characterised by clinical signs such as exercise intolerance, dyspnoea, fatigue or cough. The evaluation of the severity of these symptoms is always more or less subjective. However, the subjectivity impact was minimised in the present study by several indices, as in most previously published veterinary ACEi field studies (COVE, IMPROVE, BENCH and FIRST): use of 3- or 4-grid numerical scales for clinical parameters, evaluation of each dog over time always performed by the same investigator, relatively long follow-up period (three months), blind conditions.

The success rates after three months of follow-up were 66 per cent for imidapril versus 68 per cent for benazepril, respectively. In addition, the overall efficacy was assessed as at least satisfactory by the investigators in 85.5 per cent of the cases for imidapril versus 83.3 per cent of the cases for benazepril and by the owners in 81.2 and 78.9 per cent of the cases for imidapril and benazepril, respectively. Therefore, since the treatment group baselines were comparable, it was concluded that imidapril was as efficient as benazepril at the dose of 0.25 mg/kg once a day.

Furthermore, the adjusted “success rates” were 70.0 and 75.0 per cent in the naïve group and 55.0 and 50.0 per cent for the pre-treated dogs, respectively, in the imidapril and benazepril groups. The marked difference observed between both strata could be explained since an improvement of the NYHA stage and/or of the functional signs was far less likely
to be observed when continuing an ongo-
ing ACEi treatment than when initiating this treatment for the first time. Neverthe-
less, the improvement of pre-treated dogs is still very satisfactory.

The most probable explanation is that dogs for which the heart failure condition was not well controlled by the use of an ACEi were more likely to be included in the study than dogs with well-adapted therapies. Implementation of a new ther-
apy can also have a placebo effect on the owner’s assessment but not on the investi-
gator’s assessment, especially after three months of follow-up. Better treatment compliance could also partly explain the improvement. Actually, treatment compli-
ance was very accurate in both treatment groups, 96-1 and 96-9 per cent of the rec-
ommended dose in the imidapril group and in the benazepril group, respectively.

Figure 1 presents the evolution of the distribution of dogs in the different NYHA classes. The observed evolution was similar for both groups, with an important increase in the number of dogs in class 1 and a more reduced increase in class 4. This evolution indicates that over the three months of follow-up, the NYHA class was modified by the treat-
ment for several dogs, with mainly an improvement (increase of the class 1 fre-
quency) but also with some worsening (increase of the class 4 frequency), corre-
lated with the decrease of the number of dogs in the intermediate classes. This finding confirmed the primary clinical endpoint.

Regarding safety, 50-0 and 48-6 per cent of the dogs (35 dogs in each group) in the imidapril and benazepril groups, respectively, experienced at least one AE over their follow-up. These results were not surprising when one considers the pathology and the inclusion criteria. Therefore, most AEs reported by the investigators were due to aggravation of heart failure. The occurrence of the reported serious or non-serious AEs was not significantly different between treat-
ment groups. The biochemical side effects that were reported in human medicine, such as increased blood potassium values (Ferguson and Vlassés 1981, Romankiewicz and others 1983), were not observed in this study.

Finally, the findings regarding both efficacy and safety were similar to the outcome of a similar study comparing imidapril against enalapril (FIRST study, Amberger and others 2003).

As many other large European field studies, the EFFIC study presents with some limitations. The high number of investigators increased the heterogeneity of clinical examinations. However, in a given investigational site, a single investi-
gator was performing clinical examinations for both treatment groups under blind con-
ditions; thus, no group could be disadvan-
taged. In order to limit bias, only good clinical practice and cardiology-trained cli-
nician investigators were enrolled; they included the dogs complying with the inclusion/non-inclusion criteria according to their knowledge and background.

Blind conditions and randomisation were also implemented in order to limit bias. The double-placebo method would have been more adapted, but due to the very different formulations of the two study products (a freeze-dried powder for oral solution and a tablet), the develop-
ment and production of placebo for both products would have been very diffi-
cult, especially for making them unrecog-
nisable from the verum product by both the clinician and the owner. Thus the dual investigator method was chosen (clinician/ drug dispenser). Breaking of the blind conditions was a marginal problem as it concerned very few dogs (two dogs in the study) and thus could not have affected the final conclusions.

In conclusion, the study hypothesis that imidapril was not inferior to benazepril in terms of efficacy is confirmed. Moreover, no difference in terms of tolerance was demonstrated between the two treatments.

Acknowledgements

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Characterized by a slow,