The objectives (of both studies, STICLO-FR and STICLO-IT) were to demonstrate,

- efficacy of stiripentol as add-on therapy to clobazam and valproate in children with SMEI and refractory seizures,
- to study the safety profile of the combinations (or acceptability of STP)
- to document steady state concentrations of stiripentol & concomitant medications.

The studies had identical designs although STICLO-IT followed the French study in temporal sequence and could be considered a confirmatory study.

Outcomes/endpoints

The primary outcome in both studies was:

- The number of responders in each group - defined as those with >50% reduction in the number of seizures during the treatment period (2nd month).

The following were defined as secondary efficacy criteria:

- The percentage of children whose number of seizures (generalised) decreased by at least 50% in the 2nd month compared to baseline on a 30-day basis
- Percentage of children withdrawn from the trial
- Number of seizures during the comparison phase (each month separately) compared with number of seizures during baseline
- Time elapsed until the same number of seizures as in the baseline period was experienced.

Sample size: was low, limited to 100 patients or an inclusion period of 18 months. However, this choice was arbitrary.

Randomisation

The primary population for the STICLO-ITALY study was the ITT (intended to treat) population and included all patients who were randomised into the study. The primary population for the STICLO-FRANCE study was all patients randomised, apart from one patient who was considered not evaluable.

Blinding (masking)

Adverse effects related to drug interactions required, as per protocol, a reduction in dosage of comedication in many stiripentol-treated patients. This may have resulted to some degree in loss of blinding.

Statistical methods

The primary endpoint and the percentage of patients who had at least a 50% reduction in seizure frequency were analysed using the chi-squared test.

The number of seizures and percentage change from baseline in the number of seizures were analysed non-parametrically using the Mann-Whitney test.

RESULTS

Participant flow

The participant flow was the following:

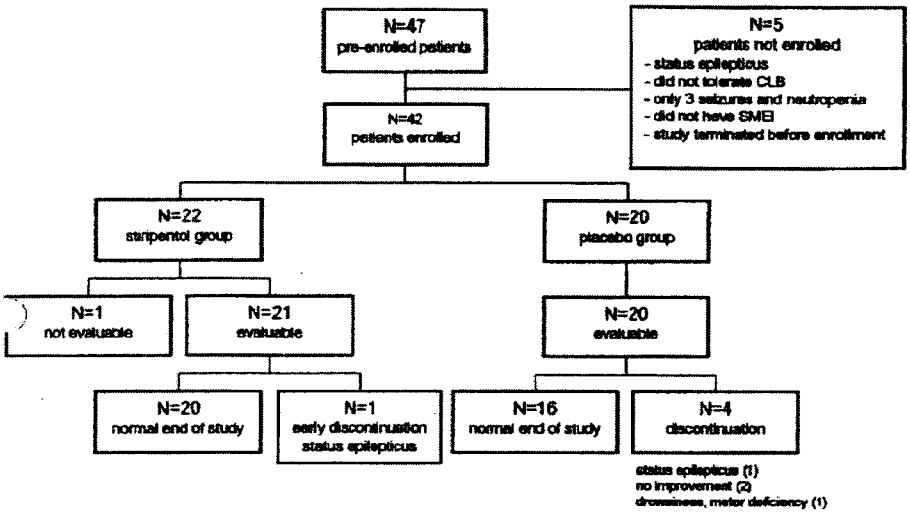

Fig 5- STICLO –France study

STICLO France study was interrupted prematurely after inclusion of 42 patients, when preliminary results showed benefit. It was followed by the STICLO Italy study, which included 23 patients.

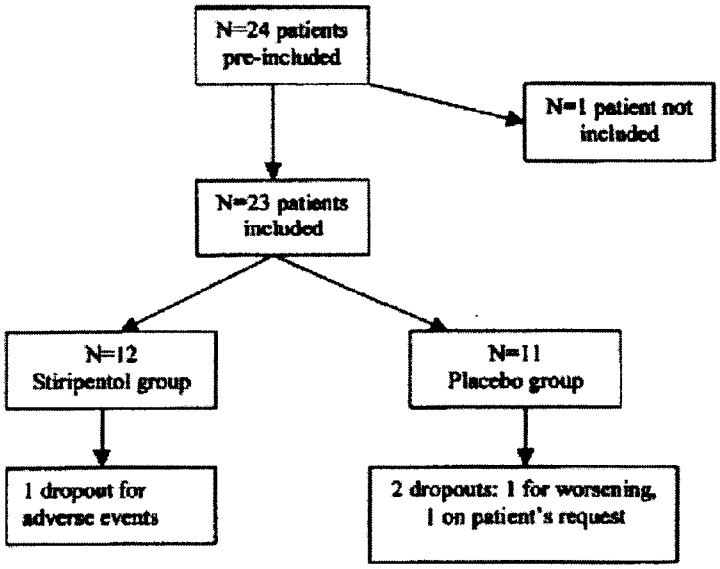

Fig-6 STICLO-IT participant flow.

Recruitment

As is evidenced from the attached graph, the recruitment in the STICLO-Fr study was gradual and apparently smooth. Data from the Italian study are not available.

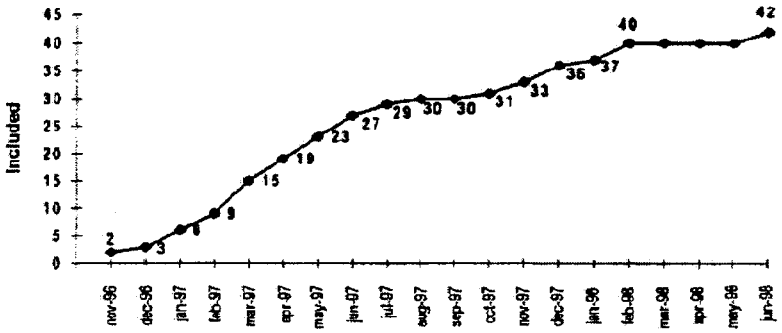

Fig 7: Recruitment pattern in STICLO-FR study.

Conduct of the study

STICLO-Fr study; as expected, there were several protocol amendments during the trial. The first was in May 1997, 7 months after start and after 20 patients had been enrolled. There were two main changes.

- First was in the inclusion criterion- upper dosage limits for valproate (20mg/kg/day before and 15mg/kg/day on entry) were removed. This was aimed to better protect the enrolled children from risk of increased seizures.
- Change in the primary end point and criteria for withdrawal; the primary end point was changed from a quantitative to a qualitative measure (success or failure). This apparently permitted the possibility to retain patients in the analysis who would have been withdrawn from the study before the comparison period.

STICLO-IT study; there were no amendments to the protocol in this supplementary study.

There were no major protocol violations.

Baseline data

Table- 18: Patient characteristics;

		STICLO-Fr		*STICLO -IT*	
		STP (n=21)	Placebo (n=20)	*STP*	*Placebo*
Gender (M/F)		6/15	11/9	*8/4*	*5/6*
Age (mean±SD)		9.4 ±4	9.29 ±4.86	*9.17±3.63*	*8.72 ±4.43*
Weight		31.8±12.7	30.5±14.4	*31.9 ±11.7*	*29.2 ±9.04*
Seizures (N=patients)					
▪ Tonic-Clonic (uni or bilateral)		22 (4 + 18)	20 (1 +19)	*14 (4+10)*	*14(5+9)*
▪ Atypical Absence		11	9	*3*	*5*
▪ Myoclonus		10	11	*13*	*11*
▪ Other		2	4	*1*	*1*
Number of seizures /month		17.9±17.3 (3.9 to 72.9)	18.5±17.0 (4.1 to 76.2)	*33.6 ±28.2 2.14 to 86.1*	*27.4 ±28.6 3.75 to 101*
Clinical findings				*NA*	*NA*
▪ Normal		20	19		
▪ Neurological abnormality		12	10		
▪ Pyramidal syndrome		(4)	(1)		
▪ Mental retardation		21	20		
▪ Behavioural disorders		15 (2 severe)	15 (6 severe)		
No of Previous Treatments		6.6±2.5 3-11	7.5±2.9 3-13	*NA*	*NA*
AED doses (pre-inclusion) (mg/kg/day)					
▪ Sodium Valproate		23.6±9.47	24.04±8.53	*28.2 ±7.98*	*25.3 ±7.0*
▪ Clobazam		0.532 ±0.247	0.55 ±0.27	*0.575± 0.21*	*0.538±0.18*
▪ Pts on Progabide		5 (23.8%)	2 (10%)	*NA*	*NA*
▪ Occasional Diazepam		3 (14.3%)	2 (10%)	*NA*	*NA*

The distributions of most characteristics at baseline were similar between stiripentol and Placebo groups in both studies. Some data such as clinical examination findings and previous treatments are only available in the first, STICLO-Fr study. The table represents selected important baseline characteristics. Other features such as AEDs at baseline (visit-2), laboratory parameters at baseline and the minimum plasma concentration of AEDS were comparable in the stiripentol and the placebo groups. The number of subjects with different types of seizure activity showed minor differences. These seizure activity types were not mutually exclusive and could co-exist in the same individual and hence there is overlap of numbers/frequencies. There were more children with severe mental retardation in the placebo group in STICLO-France study, while the overall numbers were equal.

Numbers analysed

In the STICLO-France study, 41 subjects (of 47 screened were analysed); 21 in stiripentol group and 20 in placebo group. There were 5 discontinuations (see participant flow above for the reasons for discontinuation). The ITT population comprised therefore of 41 subjects.

In the STICLO-Italy study, of the 23 evaluable patients, there were 3 dropouts; 2 in placebo group and I in stiripentol group. The ITT population of 23 subjects were analysed.

Outcomes and estimation.

Primary end point:

The table shows the number of responders in each of the pivotal trials;

Number of responders

		Responders		95% confidence interval
		Numbers	Frequency	
STICLO-Fr				
	Stiripentol	15/21	71.4%	52.1- 90.7%
	Placebo	1/20	5%	0.0-14.6%
STICLO-IT (ITT)				
	Stiripentol	8/12	66.7%	34.9 -90.2 %
	Placebo	1/11	9.1%	0.0-41.3%

Secondary Endpoints

Variation in Seizures with treatment in STICLO studies

	STICLO-Fr (all randomised)			***STICLO-IT (PP population)***		
	STP (n=21)	PLA (n=20)	Chi Sq	*STP (n=11)*	*PLA (n=9)*	*Chi Sq*
No seizures (100%)	9 (45%)	0	P<0.01	*3 (27%)*	*0*	*P~0.05*
Decrease >50 <100%	6 (30%)	1 (6%)		*5 (45%)*	*1 (11%)*	
Decrease <50%	3 (15%)	5 (31%)		*3 (27%)*	*7 (78%)*	
Increase <50%	2 (10%)	8 (50%)		*0*	*0*	
Increase >50%	0	2 (13%)		*0*	*1(11%0*	

The results for the percentage change of seizure frequency from baseline are shown in the tables below.

Mean (SD) seizure frequency – STICLO FRANCE

	Stiripentol	Placebo	p-value
1.4.1 Baseline			
Number of seizures	17.9 (17.3)	18.5 (17.0)	
1.4.2 Month 1			
Number of seizures	2.72 (4.06)	23.82 (36.55)	p<0.001
% change from baseline	-83.2 (28.0)	+11.3 (54.7)	p<0.001
1.4.3 Month 2			
Number of seizures	5.15 (7.73)	13.80 (7.33)	p<0.002
% change from baseline	-68.6 (41.9)	+7.4% (37.6)	p<0.002
Seizure-free patients	9/20 (45%)	0/16	p=0.0013

Mean (SD) seizure frequency – STICLO ITALY

	Stiripentol	Placebo	p-value
1.4.4 Baseline			
Number of seizures	33.6 (28.2)	27.4 (28.6)	
1.4.5 Month 1			
Number of seizures	4.7 (7.3)	29.0 (35.6)	p=0.0003
% change from baseline	-89.5 (15.7)	+5.5 (55.4)	p<0.05
1.4.6 Month 2			
Number of seizures	9.8 (10.0)	16.7 (11.3)	p=NS
% change from baseline	-74.3 (26.3)	-12.7 (61.9)	p=NS

Seizure-free patients	3/11 (27%)	0/9	p=0.05

Primarily, tonic-clonic seizures were assessed. The applicant has provided evidence that other types of seizures did not worsen albeit data are very limited. The applicant and the experts provided justification that status epilepticus would not be a good end point and this is acceptable. In the STICLO-FR *study*, there was a decrease of seizures by (-) 83±28% for stiripentol group, while there was an increase in placebo group (+11.3±54.7%) during the first month. For month-2 these were, -68.6±41.9% (baseline to M-2, STP) and an increase of +7.37±37.6% (Placebo). In the STICLO-IT study, there was a decrease of 89±15% for stiripentol while the placebo group showed an increase of 5.5±55% in M-1. For month-2 (M2), the corresponding figures were 74±26% and 12.7±61.9%, respectively, both stiripentol and placebo showing a decrease in frequency.

- Analysis performed across trials (pooled analyses and meta-analysis)

In neither of the studies, an analysis by centre was feasible (2.9 subjects per centre on average) because of the small numbers. No sub-group analyses or multiple comparisons were made.

- Clinical studies in special populations

SMEI is the target population where indication is sought and the two pivotal studies included patients with SMEI. There were no studies in special populations such as those with renal or hepatic insufficiency.

- Supportive study(ies)

There are 4 controlled and 3 open studies and approximately 280 patients who received at least one dose of stiripentol in the controlled studies. The main theme through out the development programme has been the use of stiripentol in combination with other anticonvulsants and not as monotherapy. The primary efficacy criterion has also been either a qualitative reduction in severity of seizures or an overall reduction in number of seizures.
The STEV study provided the basis for the hypothesis that stiripentol might be effective in SMEI. This 2-centre, 2-phase study included 43 (of 233, 18.9%) myoclonic epilepsy patients and 25 (11%) specifically SMEI. In total 157 completed the study and there were 76 withdrawals. The response rates in SMEI differed in the two phases; 27.9% in first 28 days (phase-1) and 18.6% in the next 28 days (phase II). Other interesting observations included that stiripentol seemed more effective in those older than 9 years in the ITT groups but those older than 3 years for the PP population. The lack of continued efficacy over a period (from phase I to phase II) does appear to be an issue in the pivotal trials (STICLO studies, month-1 to 2 comparisons) and persists in the STILON study.
The open STILON study included those with good response to stiripentol in the previous studies (STICLO, WOW, STICAR etc) and those who were willing to pursue stiripentol, thereby providing a rather select population. All types of epilepsy were included and a maximum dose of stiripentol of 4000 mg/day was permitted. There were no restrictions on the anticonvulsant co-medications. There were 45 patients with SMEI. The dose of stiripentol varied as the investigators were permitted to alter these based on clinical effect. Nearly a third of all patients (51 of 155) withdrew and 17 were due to lack of efficacy. The response calculated as RR index varied between different forms of epilepsy and in SMEI the index was 0.03±0.61. In this study the doses of stiripentol varied and there were very few patients who received doses >60mg/kg/day in the SMEI group. A third (31.6%) were administered doses lower than the pivotal studies (40mg/kg/day). Hence these data do not support incremental doses.

- **Discussion on clinical efficacy**

Although efficacy in animal models has been claimed, the anti-epileptic activity of stiripentol has not been demonstrated clinically since stiripentol monotherapy has not been studied in the target indication of Dravet's syndrome or severe myoclonic epilepsy of infancy (SMEI). The major mechanism of benefit of stiripentol in man appears to arise from its interactions with other, co-administered anti-epileptic agents.

The two placebo-controlled pivotal studies in the indication of interest (STICLO France and STICLO Italy), included a small number of patients (65 only in total, including patients randomised to placebo). All patients received a combination of clobazam and valproic acid with a fixed dose of 50 mg/kg/day of stiripentol. The duration of double-blind treatment and assessment was limited to two months only. The efficacy was evaluated only on clonic and tonic-clonic types of seizures. The impact of treatment on psychomotor development (a major concern in this population) was not determined and would have required a longer duration of assessment.
There are no dose response data (fixed dose only studied) and the evidence of maintained efficacy on continued use is not forthcoming from these trials.

There were significant differences in seizure frequencies between stiripentol-treated patients and the placebo group in the short-term, with a highly significant difference in primary efficacy endpoint in favour of stiripentol. However, despite a mean 38% reduction in clobazam dosage, the serum concentrations of clobazam and its active metabolite norclobazam increased markedly in the stiripentol group.
While in STICLO France clobazam and norclobazam levels at baseline were similar in the two groups, during double-blind treatment clobazam and norclobazam levels were on average 50% and 450% higher in the stiripentol group than in the placebo. Similar changes, though of a slightly different magnitude, were observed in STICLO Italy.

It is therefore plausible that the reduction in seizure frequency observed during stiripentol treatment could be ascribed entirely to the increase in the concentration of clobazam and its active metabolite. Such an increase in clobazam dose might have achieved the same effect without exposure of the subjects to the added intrinsic toxicity of stiripentol.
Additionally, a pharmacokinetic interaction with valproate may contribute to the effects seen after stiripentol administration. Changes of valproic acid levels in the two groups were less prominent, but serum unbound valproic acid concentrations were not determined, which limits ability to draw conclusions about the possibility of a pharmacokinetic interaction also occurring with valproic acid.

Therefore, comparison of addition of effects of stiripentol to maximum safe doses of co-medications (clobazam+valproate) is needed. Consequently at the request of the CHMP, the applicant committed to provide as a specific obligation (see below), a clinical study where, the doses of clobazam and valproate are increased to the maximal tolerated level in the control group, in line with the changes that occur in the active group. Dose alterations will be achieved in stringently blinded fashion preferably. The study is expected to assess the comparative effect of stiripentol vs. placebo over 12 weeks. An outline of the protocol is given below:

Randomised placebo-controlled trial using stiripentol (STP) as an add-on therapy in paediatric patients with Dravet's syndrome (SMEI) not adequately controlled with clobazam and valproate.

Double-blind, placebo-controlled trial in adjunctive therapy
Multicenter European study, including approximately 40 patients.

Primary objective:
To evaluate the efficacy of STP in the control of seizures when used as an add-on therapy in paediatric patients with Dravet's syndrome not adequately controlled with clobazam and valproate.

Secondary objectives:
- To evaluate the stiripentol efficacy on generalized (tonic)-clonic seizures (percentage of change in seizure frequency) during the four months of the treatment period (including one month of adaptation of the comedications and three months of comparison period), compared to baseline.
- To evaluate the percentage of responders (defined as having more than 50% decrease in seizure frequency) during the four months of the treatment period (including one month of adaptation of the comedications and three months of comparison period), compared to baseline.
- To evaluate the percentage of responders (defined as having more than 50% decrease in seizure frequency) during the three months of the treatment period compared to baseline.
- To evaluate the safety of stiripentol as adjunctive therapy to clobazam + valproate when compared with maximum safe dose of clobazam + valproate.

- To evaluate the number of patients who drop out due to status epilepticus and/or severe adverse events during the double-blind period.
- To describe the effect of stiripentol on myoclonia and absences (scores during the three months of the comparison period compared to scores during baseline)

Diagnosis and main criteria
- Children aged 6 months to 15 years
- Diagnosis of SMEI (Dravet's syndrome)
- Treatment with valproate and clobazam at the maximum safe dose

Supportive studies
The supportive studies were done in a non-homogeneous population of patients, with disparate designs in terms of follow-up, the co-medications, and primary end point definitions.
In STEV and STILON studies, a small number of SMEI patients were included, but the combinations differed, as did the response rate: ~20% in STEV (27 and 18.9% for periods 1 and 2) and about 15% in STILON. In STILON study, there was some reduction in the number of subjects experiencing up to 10 seizures a month (11% reduction).
These studies do not provide sufficient evidence of efficacy and are not pertinent to the claimed indication.

The STILON study, that used stiripentol on compassionate grounds, and allowed extended open-label stiripentol treatment in patients completing the STICLO studies (as well as patients receiving stiripentol in other protocols) is the only study providing data on long-term follow-up in the target indication. Unfortunately, the information that can be obtained from this study is limited due to its uncontrolled design and the loss of about one third of patients to follow-up for efficacy evaluation.

Clinical safety

The clinical safety analyses have included all studies involved in the clinical development (mainly in France). The initial studies were open trials in patients with "refractory epilepsies" and the controlled studies were performed later.
There is a significant diversity in the study designs dating back to 1976; this diversity includes indications, the patient population and doses of stiripentol, thereby limiting the ability to pool data across studies.

- Patient exposure

Due to the diversity among studies and doses used, it is not feasible to summarise or compute exposure according to dose or exact duration of exposure. Stiripentol was always administered orally but two different formulations (capsules or sachets) with (possibly or presumably) different bioavailabilities were employed. At the request of the CHMP, the applicant committed to perform a new bioequivalence study between capsules and sachets, in post-authorisation as a specific obligation (see clinical PK section)
The exposure is therefore assessed in 3 formats; pivotal studies (fixed dose), other studies (open and preliminary) and lastly post marketing experience.
In the pivotal, controlled studies, ~60 patients were exposed a dose of 50 mg/kg/day; in preliminary studies, a total of ~430 patients were included with about 80 receiving stiripentol for about 2 years. In the post marketing use, ~250 patients have been exposed to stiripentol but doses are difficult to calculate.
The proportion of patients receiving doses higher than 50 mg/kg/day can not be computed with any certainty from the dossier. More than 50% had approximate stiripentol exposure of 2 years and nearly 80% of SMEI group had 2 years or more exposure. Calculation of total exposure (original study period + STILON) increased the duration considerably; max duration of 18.4 years, with a mean of 6.21±1.44 years in SMEI; 8.59±3.84 for partial epilepsy.

- Adverse events

The safety summary analyses a total of 447 patients included in the pivotal studies and 475 patients from preliminary and /or non-pivotal studies (364 from studies including children). This analysis is clearly limited as adverse events were not reported by body system in all clinical studies. The coding system used diverse classifications. A number of studies reported only side effects (possibly related to study drug). These were also not separated by seriousness of the event.
The overall number of adverse events reported for all systems was higher in the STILON study (n=309 for 155 patients) over a period of 3 years (mean duration of follow-up) than the short-term STICLO studies (n= 72 and 33 events for stiripentol; 30 patients-STICLO-France, 16 and 9 for placebo grp; 29 patients, STICLO-Italy). These data are summarised in the table below:

Table-32: Adverse events by systems in the Pivotal studies

	STICLO France		*STICLO-Italy*		STILON
	STP (n=22) (50mg/kg)	Pla (n=20)	*STP (n=12) (50mg/kg)*	*Pla (n=11)*	STP (n=155) 4000mg/day
Total (CNS)	37	6	*17*	*8*	119
All body	2				*37*
CVS					*3*
GI	22	8	*14*	*1*	*39*
Laboratory Abn	6		*1*		*15*
Metabolic					*2*
Respiratory	2	2	-	—	*51*
Skin	2		*1*		*8*
Others	1				*35*
All ADRS	72	16	*33*	*9*	309

Neurological adverse events dominate the overview in both the placebo controlled STICLO studies (n=37 and 7) and in the open STILON study (n=119). Importantly, in the STILON study there were 70 reports of convulsions or aggravated convulsions (n=62) which were not found in the controlled STICLO studies, emphasizing possibly the differences in doses used.
Gastrointestinal adverse events were the next most frequent after CNS effects and the primary were loss of appetite, weight loss in STICLO studies and anorexia in the STILON study. Weight gain was noted in the STICLO studies (5 and 4 respectively) and this was conspicuously absent in the STILON study.

Table-33; Most Commonly reported adverse events (STICLO studies).

Adverse events (n, %)	STP group		Placebo group	
	France N = 21	Italy N = 12	France N = 20	Italy N = 11
At least one central nervous system event	*19 (90%)*	*9 (75%)*	*5 (25%)*	*3 (27%)*
Sleepiness, drowsiness	15	7	2	1
Hyperexcitability, agitation	5	2	-	1
Aggressiveness [1]	3	2	-	1
Ataxia	3	1	1	2
Hypotonia	2	3	1	-
At least one gastrointestinal event	*14 (67%)*	*7 (58%)*	*7 (35%)*	*1 (9%)*
Loss of appetite	7	6	1	1
Weight loss	6	2	-	-
Weight gain	5	-	4	-
Nausea, vomiting	2	3	1	-
At least one "Other" event	*5 (24%)*	*1 (8%)*	*2 (10%)*	*0*
At least one haematological event	*6 (29%)*	*0*	*0*	*0*

[1] Includes only AE terms reported in ≥5 patients in total.

Unfortunately, the adverse events could not be consistently related to plasma levels of stiripentol.
In STICLO-France study, the relationship between AEs and Cmin (trough concentration) is reported for both stiripentol and placebo groups in the next 2 Tables.

Table: **Cmin and AE in the stiripentol group**

	Minimum AE	Moderate AE	Severe AE
Stiripentol (mg/l)	7.65 ± 1.46	9.73 ± 3.17	11.00 ± 6.84
min – max	6.60 - 9.80	7.00 - 16.20	6.00 - 18.80
Median	7.10	8.20	8.20
n	*4*	*7*	*3*
Clobazam (mg/l)	0.384 ± 0.181	0.410 ± 0.157	0.222 ± 0.018
min – max	0.144 - 0.545	0.157 - 0.606	0.204 - 0.239
Median	0.424	0.388	0.223
n	*4*	*7*	*3*
Norclobazam (mg/l)	4.52 ± 1.31	5.12 ± 1.23	3.61 ± 0.75
min – max	2.68 - 5.78	3.72 - 7.06	3.12 - 4.48
median	4.80	5.24	3.24
n	*4*	*7*	*3*
Valproic acid (mg/l)	48.0 ± 11.8	71.2 ± 26.0	82.3 ± 35.8
min – max	32.6 - 57.5	42.4 - 108.0	41.0 - 104.0
median	51.0	69.0	102.0
n	*4*	*7*	*3*

Table: **Cmin and AE in the placebo group**

	absence of AE	AE
Clobazam (mg/l)	0.186 ± 0.072	0.217 ± 0.058
min - max	0.105 - 0.295	0.147 - 0.318
median	0.167	0.211
Upper limit (95%)	0.133	0.161
Lower limit (95%)	0.238	0.274
n	*10*	*7*
Norclobazam (mg/l)	1.122 ± 0.933	0.708 ± 0.292
min - max	0.224 - 3.420	0.287 - 1.040
median	0.767	0.800
Upper limit (95%)	0.441	0.424
Lower limit (95%)	1.802	0.991
n	*10*	*7*
Valproate acid	67.1 ± 26.0	73.1 ± 38.1
min - max	41.6 - 113.0	14.00 - 115.0
median	55.4	82.00
Upper limit (95%)	48.1	36.2
Lower limit (95%)	86.0	110.1
n	*10*	*7*

A large number of aggravated convulsions (in the STILON study) occurred early and it is possible that these were not related to reduction in stiripentol dose or its toxic effect but likely related to reductions in doses of co-medications that were needed at commencement of STP. The applicant has now provided the time course of withdrawals in the STILON study. Of the 17 withdrawals for lack of efficacy, majority occurred after one year of therapy (between 1 -3 years). Notably, the number of withdrawals due to ADRs were only few and this provides some reassurance (albeit limited). These lacunae in addition to the absence of monotherapy dose response studies have implications to the SmPC and posology proposed.

- Serious adverse event/deaths/other significant events

In the controlled STICLO studies, there were 9 serious adverse events in the French component but none in the Italian study (STICLO-italy). Six of these 9 were in the stiripentol group and 3 were in the placebo group. In the stiripentol group, 4 were extreme drowsiness causally related to treatment, considered severe but not serious. The other events were status epilepticus (requiring withdrawal) and giant urticaria. The placebo group had similar events; drowsiness and motor deficiency (withdrawn),

status epilepticus (withdrawn) and repeated seizures. Five of the 9, the events improved following decrease of concomitant medication.

In STILON study, there were 98 serious adverse events (SAEs) reported by 48 patients; 45% of these were convulsion or aggravated convulsions. One 18 year old experienced severe weight loss of 17 kg (probably stiripentol related) and there were 3 deaths (as discussed below).

In all studies, a cursory assessment of SAEs appears to have been used with diverse definitions of SAEs. The preliminary studies had very poor definitions and hence firm conclusions can not be drawn. A definite pattern to the SAEs is difficult to establish based on the data available. Majority of SAEs appear to be related to convulsions (occurrence or aggravation. There do not appear to be any undue risk of death or serious SAE associated with the use of stiripentol in the doses deployed in the controlled STICLO studies. The same cannot be concluded for a lower (40 mg/kg) or higher dose >60mg/kg

Deaths
A total of 9 deaths were reported in all studies. All deaths occurred in children under 16 years of age with serious co-morbid conditions but no deaths were noted in the SMEI groups in any study. In 4 of these cases a causal relation to study drug was adjudged improbable. One was an accidental head injury. The most common diagnosis in those who died was cryptogenic partial or generalised epilepsy. Six subjects (of the nine) received carbamazepine as the other AED, while 3 had VPA, and there were 2 each of clobazam and vigabatrin.

- Laboratory findings

Haematological events were reported in the STICLO France study: 6 patients in the STP group presented with abnormalities of white blood cells or platelets at the end of the comparison period that were not present at baseline. Three patients presented with neutropenia between 1000 and 1500x 109/L, 2 patients presented with thrombocytopenia<150x109/L and 1 patient presented with eosinophilia.
In the STILON study, 6 patients experienced neutropenia and 1 patient experienced thrombopenia.
In the STEV study, 1 patient experienced an SAE of neutropenia.
Except for haematological events described above, no major abnormalities in laboratory functions were noted consistently. The absence of any clinical data in those with impaired liver function is another drawback of the program.
In the French TUA programme there were only minor elevations of gamma-GT and these were not consistent with alterations in the other enzymes (AST or AST). Furthermore, the issue of hepatic adenomas in mice has also been clarified and there are no hepatic tumours noted in the TUA programme. Whilst data are limited, these new analyses are somewhat reassuring regarding the safety issues.

- Safety in special populations

Children:
A number of preliminary and open studies included both adults and children but have not reported systematically the distinction or provided the exact number of children (≤ 16 yrs). The table below shows the distribution of children in those studies where this distinction has been reported.

Table-31; Number of Children in STP development program

Study	Age (years)		Number (≤ 16 yrs)
	Mean (SD)	Range	
STICLO Fr			
▪ STP	9.4 (4.0)	3.0-16.7	21 (100%)
▪ Placebo	9.29 (4.86)	3.2 -20.7	NR
STICLO-It			
▪ STP	9.17 (3.63)	3.7 – 15.5	12 (100%)
▪ PLA	8.72 (4.43)	3.5-18.9	NR
STILON			
▪ SMEI	10.7 (4.9)	4 - 23	38 ((84.4%)
▪ Partial Epi	22.5 (16.5)	4 - 70.3	42 (51.9%)
▪ Other	20.4 (16.3)	5-67	15 (51.7%)
STEV	6.7 (5.2)	01.-20	206 (907% ≤ 14 yrs)
STICAR			
▪ STP	28 (NR)	10-63	NR
▪ PLA	30 (NR)	10-70	NR
WOW (BC276)	33 (14)	13-63	NR
Courjon et al	22.6 (NR)	2-73	50 (37% ≤ 15 yrs)
Lennox-Gastaut	8.6 (NR)	1.5-22	19 (86%)
Farwell 1993	12 (NR)	6-16	10 (100%)

NR = not reported

Only 3 main studies included children with a diagnosis of SMEI (STICLO studies and STILON). Thus the overall exposure in children with SMEI is in about ~80 patients for <16 years (excluding STEV). The number of children exposed to stiripentol appears reasonable considering the orphan indication, especially those with SMEI.
Considering the heterogeneity of the patient populations in pivotal studies - represented by 79 patients (children/adolescent) with SMEI - and in non-pivotal studies- 475 patients children and adults) with different types of epilepsy -, is not possible to perform a formal analysis of safety according to demographic factors.
However, there were no major obvious differences in tolerability profile between children and adults. The relatively low number of patients treated, and the inability to obtain a pooled analysis of data, does not allow to make any qualified statement about association of specific adverse effects with specific variables such as age, gender, genetic background, type of epilepsy disorder, comorbidities and comedications.

- Safety related to drug-drug interactions and other interactions

Stiripentol interacts with carbamazepine, phenytoin, clobazam, clonazepam, phenobarbital and several other agents by inhibiting the CYP450 enzyme system. The adverse events related to these agents are enhanced by stiripentol because of the elevation of plasma levels of these agents. Specific adverse events have not been examined in detail. As stiripentol affects VPA metabolism minimally but limits formation of the hepatotoxic metabolite of VPA, this may be an advantage for this combination.

- Discontinuation due to adverse events

There were significant number withdrawals from the open STILON study (32.9%) for various reasons and 17 were due to lack of efficacy. This may have been due to alterations in dose (40 mg/kg/day) or to the highest dose used (100 mg/kg/day). It should be considered that these withdrawals came in the face of patients being recruited into STILON based on benefit derived during the original study (STICLO, Wow, STEV or STICAR studies). Reassuringly, deaths and adverse events did not dominate the number of withdrawals.

- Post marketing experience (compassionate use)

Stiripentol has been given authorisation for temporary use in France since January 2003 specifically in patients with SMEI. The post marketing exposure under this cohort is estimated based on an average

dose of 1500 mg STP/day. For Temporary use Authorisation (TUA, primarily patients with SMEI) the cumulative estimated treatment days were 70,733 in over 200 patients. The calculated approximate exposure was 1 year per patient. For nominative TUA (that includes other types of epilepsy) the figures were 107, 801 days in about 250 patients; approximate exposure of 14 months per patient.

Between Jan 2003 to Jun 2004 (~18 month period), there were 30 adverse events in 19 patients aged 6months to 19 years. The commonest ADRs were drowsiness, loss of appetite and weight loss. Six of these were reported as serious and 13 non serious. There have been 2 deaths (unexpected); one possibly during an epileptic seizure and second following a generalised seizure. Both were considered by investigators to be causally unlikely and improbable to be related to the study drug. The subsequent narrative becomes confusing regarding serious cases although potential for thrombocytopenia exists.

Overall, the number of adverse events reported appears to be quite low in proportion to the exposure. The exact influences determining the reporting rates are often undeterminable and spontaneous reporting rates have always been low. Hence these data for post marketing experience do not provide any greater reassurance that stiripentol risk: benefit is better than that noted in the rest of the dossier.

- **Discussion on clinical safety**

SMEI is a severe disease resistant to all forms of treatment, therefore there is a real medical need to find new AEDs able to minimize the number of seizures and consequently to optimize the patient cognitive development.
In spite of the relatively small exposure and the suboptimal quality of adverse events collection and reporting methods, overall, the adverse event profile of stiripentol does not, by itself, give rise to major concerns. Adverse events related to the compound appear to be common, affect mostly the central nervous system and the gastrointestinal tract, and they are often severe in intensity. However, they appear to be reversible, particularly with adjustments in dosage of comedication. In fact, many of the observed adverse effects are probably related to elevation in serum concentrations of associated drugs.
For the safety evaluation of stiripentol, it is important to keep in mind that the drug inhibits the cytochrome P450 isoenzyme 2C9; previous studies demonstrated that the drug markedly reduces the elimination clearance of several AEDs which include phenobarbital, phenytoin, carbamazepine; for valproate stiripentol reduces the clearance of valproate metabolites (4-OH VPA, 5-OH VPA and 4-ene-VPA,) whilst having no effect on average valproate concentrations
Data are limited or sometimes unclear regarding the relationship of adverse events with dosage, dosing frequency, dose titration rates, serum stiripentol concentrations and potential risk factors (age, type of comedication, comorbidities). No adequate studies were performed to address concerns about potential adverse effects on cognitive function, behaviour and psychomotor development.

The applicant committed to address these deficiencies in post-authorisation as FUM and Specific obligations as well as in the Risk Management Plan.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which was assessed.

Table 1 - SUMMARY OF ACTIVITIES IN THE EU – RMP		
SAFETY CONCERN	**Proposed pharmacovigilance activities**	**Proposed Risk minimisation activities**
Possible renal adverse effects and hepatic effects in humans	Treatment with Diacomit must be excluded for patient with hepatic and renal impairment and liver function tests should be checked on a regular basis	SPC 4.2 and 4.4 PL 2 and 4
Potential for reproductive toxicity	Caution should be exercised when prescribing stiripentol to women of childbearing potential (adolescents) and efficient methods of contraception should be considered	SPC 4.6 PL 2
ADVERSE EVENTS		
Appearance of gastrointestinal disorders	Specific attention should be paid to the growth rate in children under treatment with stiripentol and valproate	SPC 4.4 PL 4
Frequency of neurological problems	Close monitoring of doses of drugs frequently used with stiripentol such as clobazam	SPC 4.2 and 4.4 PL 4
Some cases of neutropenia	Investigation of haematological changes (neutropenia) should be performed regularly	SPC 4.2 and 4.4 PL 4
DRUG INTERACTION		
STP enhanced the myorelaxation caused by diazepam	Diazepam and chlorpromazine should be added to the list of drug combinations requiring precautions	SPC 4.5 PL 2
STP enhanced the central depressant effect of chlorpromazine	The enhancement of the central depressant effect should be drawn to the attention of the prescriber.	SPC 4.5 PL 2
Influence of other antiepileptic drugs on stiripentol pharmacokinetics is not known	A warning should be introduced. The effect of other antiepileptic drugs on stiripentol pharmacokinetics is not known	SPC 4.5 PL 2
Impact on STP metabolism of macrolides and azole antifungal agents and impact of STP on their metabolism are not known	A warning should be introduced : The impact on STP metabolism of macrolides and azole antifungal agents, that are known to be inhibitors of CYP3A4 and substrates of the same enzyme, is not known, neither is the effect of STP on their metabolism.	SPC 4.5 PL 2

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

The applicant committed to establish an EU wide post-marketing surveillance study on safety issues including specific concerns identified by the CHMP as necessary to be monitored i.e. failure to thrive, neutropenia and hepatotoxic potential, psychomotor development and behaviour.

1.5 Overall conclusions and benefit/risk assessment

Quality

There are no unresolved quality issues that could have a negative impact on the benefit / risk balance.

Non-clinical pharmacology and toxicology

Pharmacology
In vitro and in vivo experiments demonstrated that stiripentol itself has pharmacodynamic activity consistent with a potential therapeutic effect in the proposed application. This consisted of inhibition of glycine and GABA uptake by synaptosomes. The R(+) enantiomer was more potent by a factor of two.
This however, is probably a minor component of the anticonvulsant activity of stiripentol, which is considered to result mainly from the inhibition of enzymes responsible for the metabolism of existing anti-epileptic medications.
There were no findings of clinical concern in a full programme of safety pharmacology studies.

Pharmacokinetics
The ADME profile of stiripentol has been adequately characterised.
Stereoselective processes in the GI tract lead to an enrichment of the S(-) enantiomer in plasma. Stiripentol both inhibits (rat brain cytochrome P450-mediated naphthalene hydroxylase inhibition) and induces (CYP1A2, 3A, 2C) enzyme activity.

The few toxicokinetic data indicate that safety margins with respect to adverse effects observed in toxicity studies are low or non-existent. Unfortunately, these are based on Cmax, there being no measurement of AUC. Nevertheless, there are no issues of potential clinical concern.

Toxicology
A full programme of toxicity studies has been submitted. The only finding of potential clinical concern was the formation of hepatocellular adenomas and carcinomas in the mouse carcinogenicity study. In spite of the lack of any exposure margin at the NOEL, the CHMP concluded that, considering the relatively weak oncogenic potential and the known mechanism, together with the proposed indication, the risk:benefit was acceptable with a suitable statement in the SPC.

Efficacy

Efficacy of stiripentol has been shown in specific combination with clobazam and valproate at a fixed dose of 50mg/kg/day on tonic-clonic epilepsy in SMEI in a small number of patients in two pivotal trials. Incremental doses proposed are virtually without any data. The evidence that efficacy of stiripentol is maintained in this situation beyond 2 months (long term) is unconvincing based on the available data and analysis. The effect on other forms of epilepsy in SMEI is unknown or has not been analysed.

These studies were seriously flawed by failure to take into account, in their design, the prominent pharmacokinetic interactions known to occur between stiripentol and the associated antiepileptic drugs. Most notably, no attempt was made to keep comparable concentrations of comedications in the two groups. Therefore, results do not allow to exclude that the improvement in seizure control in the stiripentol-treated groups were, in fact, purely a consequence of increased serum levels of associated drugs, particularly clobazam and its active metabolite norclobazam.
The STILON study, which allowed extended open-label stiripentol treatment in patients completing the STICLO studies (as well as patients receiving stiripentol in other protocols) is the only study providing data on long-term follow-up in the target indication. This study was less than optimal due to its uncontrolled design and loss of about one third of patients to follow-up for efficacy evaluation.

Safety

Overall, the adverse event profile of stiripentol does not, by itself, give rise to major concerns. Adverse events related to the compound appear to be common, affect mostly the central nervous system and the gastrointestinal tract, and they are often severe in intensity. However, they appear to be reversible, particularly with adjustments in dosage of co-medication.
From the safety database all the adverse reactions reported in clinical trials and post-marketing (temporary use authorisation) have been included in the Summary of Product Characteristics.

Data on safety issues including specific concerns identified by the CHMP as necessary to be monitored i.e. failure to thrive, neutropenia and hepatotoxic potential, psychomotor development and behaviour will be monitored in an EU wide post-marketing surveillance study.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The results the readability testing performed on Diacomit are satisfactory.

Risk-benefit assessment

The effect of stiripentol has been shown in specific combination with clobazam and valproate at a fixed dose of 50mg/kg/day on tonic-clonic epilepsy in SMEI in two pivotal trials. Some limited evidence that in the open phase, Stiripentol retains its effectiveness is available. There is some reassurance albeit limited, of long-term effect during follow-up in the target indication.
However, the studies are limited in assessing relative contribution of stiripentol to seizure control in SMEI. In order to address the concern that placebo group received submaximal doses of clobazam and valproate in the STICLO studies and same effect may have been achieved by simple increase in clobazam and valproate concentrations, the applicant has agreed to provide a commitment to conduct a pivotal efficacy study using maximal tolerated doses. A synopsis of the protocol is available and the applicant seeks to obtain scientific advice and protocol assistance from CHMP for such a study.

Whilst the number of adverse events reported do not raise concern overall, safety of stiripentol in man has been demonstrated only in a limited fashion. The applicant only proposes 50mg/kg dose and the higher doses initially proposed in the SPC have been withdrawn. The adverse events cannot be correlated with plasma levels adequately and hence cannot be relied upon as a guide to therapy. Despite this lacuna, as the data on the fixed dose of 50mg/kg/day do not raise major safety concerns and therefore, safety issues could be considered resolved, albeit with limited data. This is addressed in the Risk Management Plan and reflected in the SPC with appropriate restrictions.

The follow-up measures (FUMs) and specific obligations (SO) that the applicant committed for, include:

- A randomised placebo-controlled trial using stiripentol as an add-on therapy in paediatric patients with Dravet's syndrome (SMEI) not adequately controlled with clobazam and valproate by 2009 (SO).
- A bioavailability study of stiripentol after single oral administration of two 500mg formulations (capsule and sachet) in 24 healthy male volunteers to determine the relative bioavailability of the stiripentol sachet versus stiripentol capsule by 2007 (SO).
- A population pharmacokinetic study in Dravet's syndrome (SMEI) patients treated with stiripentol, valproate and clobazam (FUM).
- An *in vitro* study investigating enzymes that catalyse phase-1 reactions for predictions of possible effects of other drugs on stiripentol (FUM).

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further the following safety concerns through:

- A close monitoring of gastro-intestinal problems is needed particularly when stiripentol is combined with valproate.
- A close monitoring of doses of drugs frequently used with stiripentol such as clobazam in relation to the frequency neurological problems.

In addition, the applicant committed to establish an EU wide post-marketing safety study to collect data on safety issues including specific concerns identified by the CHMP as necessary to be monitored i.e. failure to thrive, neutropenia and hepatotoxic potential, psychomotor development and behaviour.

No additional risk minimisation activities were required beyond those included in the product information.

The CHMP considers, that stiripentol falls within the scope of Regulation (EC) No 507/2006, with particular reference to Article 2 based on the following grounds:
Stiripentol has been designated as orphan medicinal product for its use in severe myoclonic epilepsy in infants (SMEI), in accordance with Article 3 of Regulation (EC) No 141/2000, on 05 December 2001. Furthermore, SMEI is a severe disease resistant to all forms of treatment, and seriously debilitating due to the development of mental retardation in all children in the second year of life.

The CHMP considers, that Diacomit (stiripentol) fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

(a) In the two placebo-controlled pivotal studies, a significant improvement in controlling the seizure frequencies was obtained in the stiripentol group in comparison to placebo group, although further data are necessary to better characterize the clinical efficacy of stiripentol in comparison to maximally safe doses of the comedication.
The safety profile was considered acceptable.
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of stiripentol, as defined in Article 1(28a) of Directive 2001/83/EC, for the treatment of severe myoclonic epilepsy in infants (SMEI), was positive.
(b) The applicant committed to provide as a specific obligation, the results of a placebo-controlled clinical study where, the doses of clobazam and valproate are increased to the maximal tolerated level in the control group, in line with the changes that occur in the active stiripentol group. The study is expected to assess the comparative effect of stiripentol vs. placebo over 12 weeks. The CHMP considers that efficacy results from this new placebo-controlled clinical study will provide comprehensive clinical data, in particular a better understanding of the relative roles of stiripentol through its intrinsic anticonvulsant activity or through its effects on the metabolism of the adjunctive treatment with clobazam and valproate in SMEI patients. The protocol outline provides an adequate description of the planned study, including the duration of treatment (12 week). The protocol will be finalised with the support of the Rapporteurs and of a Scientific advice Procedure (protocol assistance). The final study results are expected in the 2d quarter of 2009. Thus, the CHMP considers that it is likely that the applicant will be in a position to provide the comprehensive clinical data.

(c) Among childhood epilepsies, severe myoclonic epilepsy in infants (SMEI) is one of the most deleterious epilepsy syndromes reported in the syndromic classification of the International League Against Epilepsy. The stereotyped clinical characteristics and the absence of any cerebral lesion make SMEI a nosologically and aetiologically homogeneous syndrome. Seizures appear during the first year of life and. all children develop mental retardation in the second year of life, although development is normal before that time. These seizures can never come under complete control with conventional antiepileptic drugs. Striripentol is expected to improve the control of seizures in these patients.
Therefore the CHMP considers that the unmet medical need will be fulfilled for patients with SMEI.

(d) Because seizures in SMEI never come under complete control with conventional antiepileptic drugs, the availability of stiripentol is expected to be the last alternative to improve these severely affected patients. There is evidence of efficacy in the data provided, although the role of stiripentol needs to be better understood. Therefore the CHMP considers that the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Diacomit for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate, was favourable and therefore recommended the granting of the conditional marketing authorisation for Diacomit, subject to the following specific obligations:

1. A randomised placebo-controlled trial using stiripentol as an add-on therapy in paediatric patients with Dravet's syndrome (SMEI) not adequately controlled with clobazam and valproate by 2009 (STP 165).
2. A bioavailability study of stiripentol after single oral administration of two 500mg formulations (capsule and sachet) in 24 healthy male volunteers by 2007 (STP 166).