Number of Needed to Treat (NNT) to Achieve Seizures Reduction or Seizure Freedom in Dravet Syndrome in France: Results from an ITC of Stiripentol Vs Fenfluramine and Cannabidiol and the Economic Implications

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INTRODUCTION

- Dravet syndrome (DS) is a rare and catastrophic, highly refractory developmental and epileptic encephalopathy. It is characterized by frequent, treatment-resistant convulsive seizures arising in the first years of life, followed by developmental delay and cognitive impairment, which impair patient and carer quality of life (QoL). Around 15-20% of children with DS die before reaching adulthood primarily due to status epilepticus (SE), sudden unexpected death in epilepsy (SUDEP), and accidents.
- Given the association between convulsive seizure frequency and comorbidities, quality of life, healthcare resource utilization and costs, and premature mortality described above, convulsive seizure reduction is a key goal of treatment in Dravet syndrome. Complete, sustained seizure freedom (i.e. zero convulsive seizures) is the ambition for patients with Dravet syndrome but few patients ever achieve this outcome[1].
- Recently published treatment recommendations suggest initial anti-seizure medication (ASM) with valproate or valproate and clobazam; however, as most patients' seizures are inadequately controlled with these treatments, additional add-on therapy is typically required[2]. DIACOMIT® (stiripentol)[3], FINTEPLA® (fenfluramine)[4] and EPIDIOLEX® (cannadibiol)[5] are licensed specifically as add-on ASMs for Dravet syndrome. The most recent international consensus guidelines position DIACOMIT® and FINTEPLA® ahead of EPIDIOLEX® in the treatment pathway[2].
- The number needed to treat (NNT) is an outcome measure commonly used in clinical settings, providing a quick, short-hand approach to estimating relative efficacy of different treatments. This indicator is considered meaningful for physicians and health care decision makers because it measures the number of patients that is needed to treat to prevent one additional bad outcome (e.g. death, stroke, seizures, etc.).
- The objective of this study was to evaluate the cost implications of stiripentol, fenfluramine and cannabidiol, to achieve given level of seizure reduction or freedom, using NNT.

METHODS

- NNTs, provided in table 1, are issued from the network meta-analysis published by Guerrini *et al.* 2024[6]. Relative treatment effects in the NMA were assessed using absolute risk differences (RD). The RD approach enabled the use of the largest possible dataset, ensured consistency in the presentation of the comparative treatment effect estimates, and permitted calculation of the number needed to treat (NNT) with each intervention (added on to background ASMs therapy) for one more patient to achieve the outcome of interest compared with placebo (added on to background ASMs therapy): NNT = 1/|RD|[7]. NNTs were calculated for pairwise comparisons versus placebo for RD that were statistically significant to facilitate a clinical interpretation of the NMA results.
- Annual costs per patient of the three add-on therapies are based on French prices (Prix Public Toutes Taxes Comprises PPTTC) as of June 2024 (table 2). Two patient groups are considered: pediatric patients aged 9 years with an average body weight of 30kg, based on RCTs[8] and adult patients aged 18+ years with an average body weight of 60kg[9]. The dose assumed for each of the add-on therapies is based on their approved dosing. For stiripentol, the dosing adopted in this analysis is 50mg/kg/day in pediatric patients[10] and adults[11]. For fenfluramine (used without concomitant stiripentol) this dosing is 0.7mg/kg/day (maximum 26mg per day) based on the label[12]. For cannabidiol the dosing is 20mg/kg/day[13].

Table 1. Efficacy results of pairwise comparison versus placebo[6]

Endpoints	Comparison	RCTs (N)	RD (95%CI); p-value	NNT
≥50% reduction in seizure frequency	STP vs PLB	2	RD: 0.64 (0.46; 0.81); p<0.01	NNT: 2
	FFA vs PLB	2	RD: 0.62 (0.51; 0.74); p<0.01	NNT: 2
	CBD10 vs PLB	1	RD: 0.16 (0.01; 0.31); p<0.04	NNT: 7
	CBD20 vs PLB	2	RD: 0.19 (0.08; 0.31); p<0.01	NNT: 6
≥75% reduction in seizure frequency	STP vs PLB	2	RD: 0.52 (0.34; 0.70); p<0.01	NNT: 2
	FFA vs PLB	2	RD: 0.46 (0.35; 0.57); p<0.01	NNT: 3
	CBD10 vs PLB	1	RD: 0.24 (0.12; 0.36); p<0.01	NNT: 5
	CBD20 vs PLB	2	RD: 0.11 (0.03; 0.20); p<0.02	NNT: 10
100% reduction in seizure frequency	STP vs PLB	2	RD: 0.36 (0.19; 0.53); p<0.01	NNT: 3
	FFA vs PLB	2	RD: 0.10 (0.03; 0.16); p<0.01	NNT: 10
	CBD10 vs PLB	1	RD: 0.02 (-0.03; 0.07); p=0.44	
	CBD20 vs PLB	2	RD: 0.04 (0.00;0.08); p<0.05	NNT: 25

Table 2. Annual costs for DS specific therapies in pediatric and adult patients

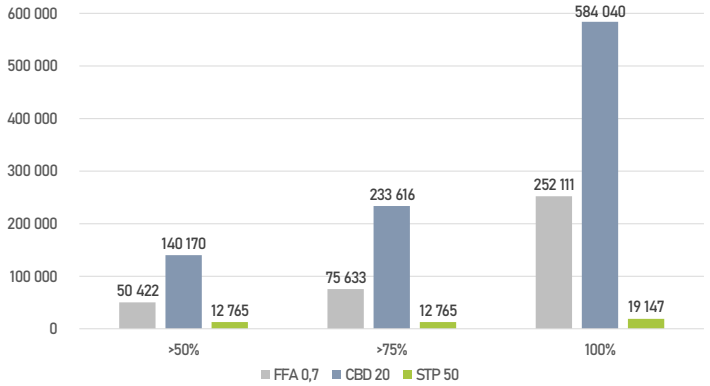
	Add on therapy initiated at age 9 years*			Add on therapy initiated in adulthood**		
	Stiripentol	Cannabidiol	Fenfluramine	Stiripentol	Cannabidiol	Fenfluramine
Dose (mg/kg/day)	50	20	0.7	50	20	0.7
Body weight (kg)	30	30	30	60	60	60
Daily dose (mg)	1500	600	21	3000	1200	26 (max)
Price per mg (€/mg)	0.012	0.107	3.289	0.012	0.107	3.289
Daily cost (€) per patient	17.49	64.00	69.07	34.97	128.01	85.52
Annual cost per patient (€)	6 382	23 362	25 211	12 765	46 723	31 214

*Assumed body mass of 30kg
** Assumed body mass of 60kg
Public prices (PPTTC) as of June 2024

RESULTS

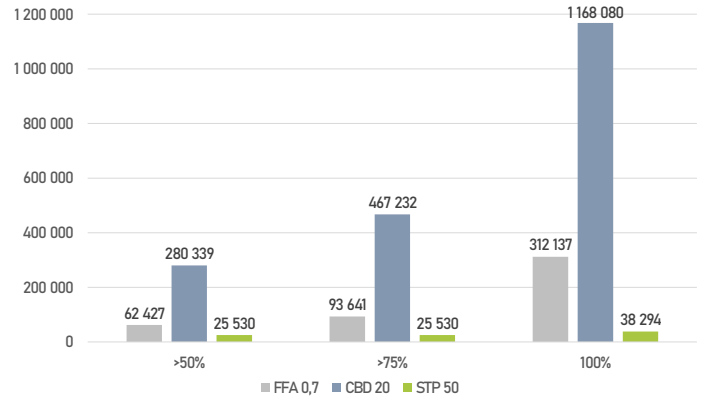
- The costs for 1 patient to achieve ≥50% (i.e., clinically meaningful), ≥75% (i.e., profound) and 100% reduction in monthly convulsive seizure frequency (MCSF) with each DS specific treatment are presented in Figure 1 for pediatric group and Figure 2 for adults.
- **In the pediatric group,** the annual costs per patient achieving a **clinically meaningful reduction in MCSF (50%)** are **12 765€ with stiripentol, 140 170€ with cannabidiol and 50 422€ with fenfluramine** and **12 765€, 233 616€ and 75 633€ respectively for the ≥75% (i.e., profound) reduction in MCSF endpoint.** Finally annual costs per patient achieving **seizures freedom** are **19 147€ for stiripentol, 584 040€ for cannabidiol and 252 111€ for fenfluramine.**

Figure 1. Annual costs per pediatric patient achieving clinically meaningful and greater reductions in MCSF



- **In the adult group**, for **the ≥50% (clinically meaningful) reduction in MCSF** endpoint the annual costs are **25 530€ for stiripentol, 280 339€ for cannabidiol and 62 427€ for fenfluramine**. The annual costs per patient achieving a **profound (≥75%) reduction in MCSF** are **25 530€ , 467 232€ and 93 641€ for stiripentol, cannabidiol and fenfluramine respectively**. Finally annual costs per patient achieving **seizures freedom** are **38 294€ for stiripentol, 1 168 080€ for cannabidiol and 312 137€ for fenfluramine**.
- In a sensitivity analysis using lower doses of the DS specific treatment in all patients and assumed similar NNT, stiripentol remained the least costly per patient achieving a clinically meaningful and profound reduction in MCSF and per patient achieving convulsive seizure freedom across all patient groups.

Figure 2. Annual costs per adult patient achieving clinically meaningful and greater reductions in MCSF



DISCUSSION

- Stiripentol has the lowest public price (PP) in France and in many countries in Europe.
- In addition, fewer patients need to be treated with stiripentol than with cannabidiol for one patient to achieve seizure reductions. Compared with fenfluramine, stiripentol is at least as effective in achieving a clinically meaningful and profound reduction in MCSF, and is more effective in achieving seizure freedom, whilst also having lower annual costs.
- This analysis shows a substantial lower annual cost with stiripentol per patient achieving a clinically meaningful and profound reduction in MCSF and convulsive seizure freedom.

CONCLUSION

Stiripentol achieves the same or better clinical outcomes at a lower cost than cannabidiol or fenfluramine. Stiripentol should be considered as a cost-effective and highly efficacious treatment for Dravet syndrome patients. These findings are observed for both pediatric and adult patient groups and in different dosages.

References:
1. Dravet et al 2011 ; Wirrell E 2016
2. Wirrell E 2022 ; NICE guidelines 2022 ; Strzelczyk A 2022
3. EMA label DIACOMIT
4. EMA label FINTEPLA
5. EMA label EPIDYOLEX
6. Guerrini et al 2024
7. Higgins J et al 2022
8. Chiron 2000, Lagae 2019, Devinsky 2011
9. World Health Organization (WHO). Weight-for-age charts Charts. 2001
10. EMA label DIACOMIT
11. EMA label DIACOMIT
12. EMA label FINTEPLA
13. EMA label EPIDYOLEX

Acronyms:
ASM: Antiseizure medications
CBD: Cannabidiol
DS: Dravet syndrome
FFA: Fenfluramine
MCSF: Monthly Convulsive Seizure Frequency
NNT: Number Needed to Treat
RCT: Randomized Clinical Trials
PLB: Placebo
PP: Public prices
PPTTC: Prix Public Toutes Taxes Comprises

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