

Yong Park,¹ Teresa Greco,² Kelly C. Simontacchi,³ Timothy B. Saurer,³ Elizabeth A. Thiele⁴¹Medical College of Georgia at Augusta University, Augusta, GA, USA; ²Jazz Pharmaceuticals, Inc., Gentium Srl, Villa Guardia, Italy; ³Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA; ⁴Massachusetts General Hospital, Boston, MA, USA

Introduction

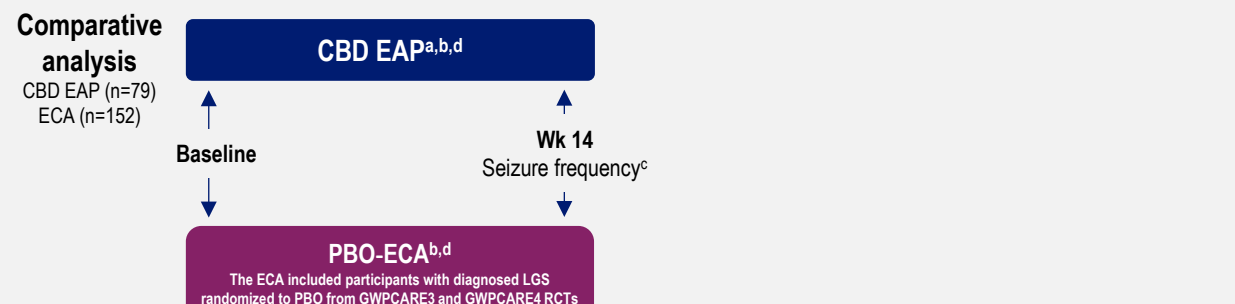
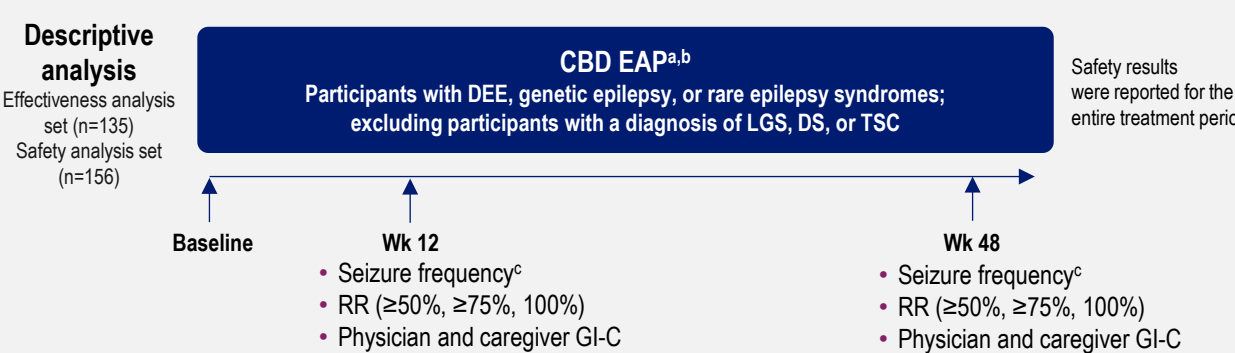
- Developmental and epileptic encephalopathies (DEEs) are a group of rare and severe childhood-onset epilepsies, marked by high seizure burden, pharmacoresistance, and disabling comorbidities, presenting several unmet clinical needs¹
- Plant-derived, highly purified cannabidiol (CBD; Epidiolex®, 100 mg/mL oral solution) is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients ≥1 year of age²
- Real-world evidence suggests that CBD may have utility in other DEEs, such as Aicardi syndrome, CDKL5 deficiency disorder, Dup15q syndrome, and epilepsy with myoclonic-atonic seizures (EPMAS)³
- The CBD Expanded Access Program (EAP) provided compassionate access to CBD for patients with diverse treatment-resistant epilepsies, including DEEs
- This post hoc analysis of the US CBD EAP evaluates seizure and safety outcomes in participants with rare and severe childhood-onset epilepsies, compared with an external placebo control arm (ECA)⁴⁻⁶

Objectives

- To describe the baseline demographics and clinical characteristics, effectiveness, and safety of CBD among EAP participants with rare epilepsy syndromes including DEEs other than LGS, DS, and TSC
- To compare the effectiveness of CBD treatment in participants with rare epilepsy syndromes to an ECA

Methods

Figure 1. Study design: Descriptive analysis of CBD EAP and comparative analysis of CBD EAP vs ECA



*Participants received CBD (Epidiolex®) doses starting at 2–10 mg/kg/day and titrated up to a maximum of 25–50 mg/kg/day at the discretion of the investigator and institutional review board at each EAP site.
†All participants enrolled in both CBD EAP and ECA had treatment-resistant epilepsy and were receiving stable doses of antiseizure medications for ≥4 weeks before enrollment.
‡Convulsive and total seizures.
§Participants with a minimum frequency of 8 convulsive seizures per 28 days during baseline were included in the analysis.
|| CBD, cannabidiol; DEEs, developmental and epileptic encephalopathies; DS, Dravet syndrome; EAP, Expanded Access Program; ECA, external placebo control arm; GI-C, Global Impression of Change; LGS, Lennox-Gastaut syndrome; PBO, placebo; RCTs, randomized controlled trials; RR, responder rate; TSC, tuberous sclerosis complex.

Descriptive analysis: CBD EAP cohort

- Participants with rare and severe childhood-onset epilepsies—including those diagnosed with DEE, genetic epilepsy, or a rare epilepsy syndrome—were included in the CBD EAP analysis cohort (Figure 1). Participants with a diagnosis or co-diagnosis of LGS, DS, or TSC were excluded from this cohort
- Rare epilepsy subgroups including Aicardi syndrome, CDKL5 deficiency disorder, Dup15q syndrome, early infantile epileptic encephalopathy (EIEE), EPMAS, febrile infection-related epilepsy syndrome (FIRES), myoclonic absence epilepsy, SCN2A-DEE, Sturge-Weber syndrome (SWS), and other genetic epilepsies were analyzed
- Rare epilepsies with <5 participants were pooled into an “other genetic epilepsies” subgroup
- Effectiveness of CBD was assessed as percentage reduction from baseline in median 28-day convulsive and total seizure frequencies at Weeks 12 and 48
- Responder rates (RRs; ≥50%, ≥75%, and 100% seizure reduction) were reported at Weeks 12 and 48
- Physician and Caregiver Global Impression of Change (GI-C) were reported at Weeks 12 and 48
- Safety results were reported for the entire treatment period (median duration, 617 days)

Comparative analysis: CBD EAP vs ECA

- A comparative effectiveness analysis was conducted using an ECA to evaluate the effectiveness of CBD in reducing the 28-day average number of convulsive or total seizure frequencies during the first 14 weeks of treatment (Figure 1)
- Participants with a seizure frequency of <8 convulsive seizures per 28 days during the baseline period were excluded
- The ECA was composed of participants with LGS who were randomized to placebo in the GWPCARE3 and GWPCARE4 randomized controlled trials
- To minimize information bias, comparability was verified in terms of eligibility criteria, treatment strategy, assignment procedure, follow-up period, measures at baseline, and endpoints⁵
- Inverse probability weighting based on propensity scores^{6,7} was applied to minimize the association between treatment exposure and study participation and balance key baseline covariates, including age, sex, concurrent seizure frequency at baseline, number of concomitant antiseizure medications (ASMs), and current clobazam use
- Assuming that no other confounding variables were associated with both the response variable and the treatment, the average treatment effect of CBD compared with placebo was estimated by performing a weighted log-transformed analysis of covariance model
- Balancing performance was investigated using a standardized weighted mean differences plot
- Absence of hidden bias was confirmed through the Rosenbaum sensitivity analysis
- This study used data from Epidiolex®, and the results of this post hoc analysis do not apply to other CBD-containing products

Results

Baseline demographics and clinical characteristics of CBD EAP participants with rare epilepsies

Table 1. Participant demographics and baseline antiseizure medications (CBD EAP effectiveness analysis set)

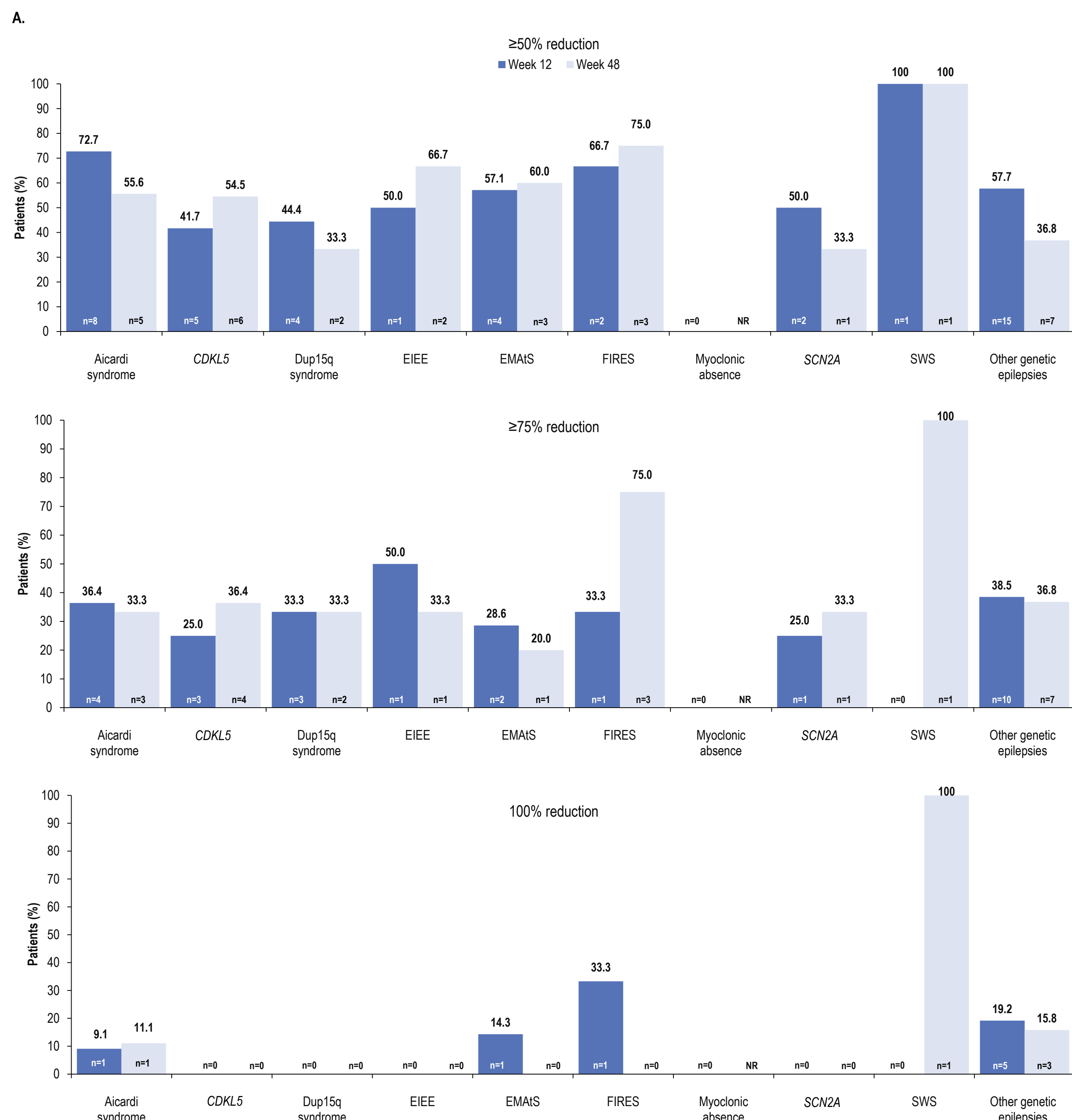
	Overall	Aicardi syndrome	CDKL5	Dup15q syndrome	EIEE	EMAS	FIRES	Myoclonic absence	SCN2A	SWS	Other genetic epilepsies ^a
N (%)	135	17 (12.6)	20 (14.8)	11 (8.1)	6 (4.4)	11 (8.1)	13 (9.6)	5 (3.7)	5 (3.7)	5 (3.7)	42 (31.1)
Age, years, Mean (SD)	9.7 (6.0)	10.2 (5.8)	6.8 (4.2)	12.4 (4.9)	6.0 (6.1)	9.5 (3.4)	9.4 (5.6)	14.4 (4.4)	5.0 (2.6)	8.9 (6.1)	11.2 (7.1)
Sex, female, n (%)	87 (64.4)	17 (100)	19 (95.0)	5 (45.5)	6 (100)	3 (27.3)	7 (53.8)	2 (40.0)	3 (60.0)	4 (80.0)	21 (50.0)
Number of ASMs, mean (SD)	2.8 (1.2)	2.5 (1.0)	2.5 (0.8)	3.0 (0.5)	3.5 (1.1)	2.8 (0.9)	4.5 (1.7)	—	2.8 (0.8)	2.6 (1.3)	2.5 (1.2)
ASMs, n (%)											
Clobazam	54 (40)	9 (53)	6 (30)	5 (46)	2 (33)	5 (45)	7 (54)	—	1 (20)	1 (20)	18 (43)
Levetiracetam	45 (33)	5 (29)	6 (30)	4 (36)	3 (50)	2 (18)	10 (77)	—	2 (40)	2 (40)	11 (26)
Valproic acid	40 (30)	5 (29)	10 (50)	5 (46)	0	2 (18)	3 (23)	0	3 (60)	12 (29)	12 (29)
Topiramate	13 (10)	0	4 (20)	1 (9)	1 (17)	0	3 (23)	—	1 (20)	1 (20)	2 (5)
Lamotrigine	28 (21)	7 (41)	5 (25)	4 (36)	0	3 (27)	1 (8)	—	1 (20)	0	7 (17)
Rufinamide	24 (18)	4 (24)	2 (10)	6 (55)	1 (17)	4 (36)	2 (15)	—	1 (20)	3 (7)	3 (7)
Felbamate	9 (7)	0	0	0	0	3 (27)	3 (23)	—	0	1 (20)	2 (5)
Seizure frequency, median (Q1, Q3), [n]											
Convulsive seizures	42 (16, 104) [100]	47 (18, 74) [14]	52 (25, 100) [18]	58 (5, 209) [11]	170 (29, 2950) [4]	61 (32, 116) [9]	60 (24, 2840) [5]	4 (4, 4) [1]	25 (13, 112) [5]	1 (1, 1) [1]	40 (4, 98) [32]
Total seizures	80 (28, 294) [135]	57 (24, 109) [17]	95 (42, 231) [20]	89 (55, 272) [11]	205 (18, 384) [11]	86 (32, 404) [11]	216 (60, 4000) [13]	2800 (1750, 2800) [5]	112 (74, 138) [5]	2 (1, 6) [5]	72 (20, 217) [42]

^aIncluded rare epilepsies affecting <5 participants, had diagnostic terms: 15q11.2 deletion, 1p36 deletion, 22q11 duplication, ADNFLE-DEPDC5 mutation, Angelman syndrome, BRAP mutation, CACNA1E mutation, CLCN4A mutation, COL4A1 mutation, deletion 16 (p13, 11p13.1), DISC1 X, Dup15q mutation, DYRK1A mutation, EPMAS, EIEE, GLUT1 deletion, GPHN mutation, GRIN2A mutation, HCN2 mutation, infantile spasms, Jervell-Lange-Nielsen syndrome, KCNA1 mutation, KCNQ2 mutation, LYPB2 haplotype deficiency, MECP2 duplication, Rett syndrome, SCN1A mutation, SCN2A mutation, SMAD3 mutation, sodium channelopathy, SYNGAP1 mutation, TSC1 and TSC2 mutation, TSC2 mutation, TSC3 mutation, TSC4 mutation, TSC5 mutation, TSC6 mutation, TSC7 mutation, TSC8 mutation, TSC9 mutation, TSC10 mutation, TSC11 mutation, TSC12 mutation, TSC13 mutation, TSC14 mutation, TSC15 mutation, TSC16 mutation, TSC17 mutation, TSC18 mutation, TSC19 mutation, TSC20 mutation, TSC21 mutation, TSC22 mutation, TSC23 mutation, TSC24 mutation, TSC25 mutation, TSC26 mutation, TSC27 mutation, TSC28 mutation, TSC29 mutation, TSC30 mutation, TSC31 mutation, TSC32 mutation, TSC33 mutation, TSC34 mutation, TSC35 mutation, TSC36 mutation, TSC37 mutation, TSC38 mutation, TSC39 mutation, TSC40 mutation, TSC41 mutation, TSC42 mutation, TSC43 mutation, TSC44 mutation, TSC45 mutation, TSC46 mutation, TSC47 mutation, TSC48 mutation, TSC49 mutation, TSC50 mutation, TSC51 mutation, TSC52 mutation, TSC53 mutation, TSC54 mutation, TSC55 mutation, TSC56 mutation, TSC57 mutation, TSC58 mutation, TSC59 mutation, TSC60 mutation, TSC61 mutation, TSC62 mutation, TSC63 mutation, TSC64 mutation, TSC65 mutation, TSC66 mutation, TSC67 mutation, TSC68 mutation, TSC69 mutation, TSC70 mutation, TSC71 mutation, TSC72 mutation, TSC73 mutation, TSC74 mutation, TSC75 mutation, TSC76 mutation, TSC77 mutation, TSC78 mutation, TSC79 mutation, TSC80 mutation, TSC81 mutation, TSC82 mutation, TSC83 mutation, TSC84 mutation, TSC85 mutation, TSC86 mutation, TSC87 mutation, TSC88 mutation, TSC89 mutation, TSC90 mutation, TSC91 mutation, TSC92 mutation, TSC93 mutation, TSC94 mutation, TSC95 mutation, TSC96 mutation, TSC97 mutation, TSC98 mutation, TSC99 mutation, TSC100 mutation, TSC101 mutation, TSC102 mutation, TSC103 mutation, TSC104 mutation, TSC105 mutation, TSC106 mutation, TSC107 mutation, TSC108 mutation, TSC109 mutation, TSC110 mutation, TSC111 mutation, TSC112 mutation, TSC113 mutation, TSC114 mutation, TSC115 mutation, TSC116 mutation, TSC117 mutation, TSC118 mutation, TSC119 mutation, TSC120 mutation, TSC121 mutation, TSC122 mutation, TSC123 mutation, TSC124 mutation, TSC125 mutation, TSC126 mutation, TSC127 mutation, TSC128 mutation, TSC129 mutation, TSC130 mutation, TSC131 mutation, TSC132 mutation, TSC133 mutation, TSC134 mutation, TSC135 mutation, TSC136 mutation, TSC137 mutation, TSC138 mutation, TSC139 mutation, TSC140 mutation, TSC141 mutation, TSC142 mutation, TSC143 mutation, TSC144 mutation, TSC145 mutation, TSC146 mutation, TSC147 mutation, TSC148 mutation, TSC149 mutation, TSC150 mutation, TSC151 mutation, TSC152 mutation, TSC153 mutation, TSC154 mutation, TSC155 mutation, TSC156 mutation, TSC157 mutation, TSC158 mutation, TSC159 mutation, TSC160 mutation, TSC161 mutation, TSC162 mutation, TSC163 mutation, TSC164 mutation, TSC165 mutation, TSC166 mutation, TSC167 mutation, TSC168 mutation, TSC169 mutation, TSC170 mutation, TSC171 mutation, TSC172 mutation, TSC173 mutation, TSC174 mutation, TSC175 mutation, TSC176 mutation, TSC177 mutation, TSC178 mutation, TSC179 mutation, TSC180 mutation, TSC181 mutation, TSC182 mutation, TSC183 mutation, TSC184 mutation, TSC185 mutation, TSC186 mutation, TSC187 mutation, TSC188 mutation, TSC189 mutation, TSC190 mutation, TSC191 mutation, TSC192 mutation, TSC193 mutation, TSC194 mutation, TSC195 mutation, TSC196 mutation, TSC197 mutation, TSC198 mutation, TSC199 mutation, TSC200 mutation, TSC201 mutation, TSC202 mutation, TSC203 mutation, TSC204 mutation, TSC205 mutation, TSC206 mutation, TSC207 mutation, TSC208 mutation, TSC209 mutation, TSC210 mutation, TSC211 mutation, TSC212 mutation, TSC213 mutation, TSC214 mutation, TSC215 mutation, TSC216 mutation, TSC217 mutation, TSC218 mutation, TSC219 mutation, TSC220 mutation, TSC221 mutation, TSC222 mutation, TSC223 mutation, TSC224 mutation, TSC225 mutation, TSC226 mutation, TSC227 mutation, TSC228 mutation, TSC229 mutation, TSC230 mutation, TSC231 mutation, TSC232 mutation, TSC233 mutation, TSC234 mutation, TSC235 mutation, TSC236 mutation, TSC237 mutation, TSC238 mutation, TSC239 mutation, TSC240 mutation, TSC241 mutation, TSC242 mutation, TSC243 mutation, TSC244 mutation, TSC245 mutation, TSC246 mutation, TSC247 mutation, TSC248 mutation, TSC249 mutation, TSC250 mutation, TSC251 mutation, TSC252 mutation, TSC253 mutation, TSC254 mutation, TSC255 mutation, TSC256 mutation, TSC257 mutation, TSC258 mutation, TSC259 mutation, TSC260 mutation, TSC261 mutation, TSC262 mutation, TSC263 mutation, TSC264 mutation, TSC265 mutation, TSC266 mutation, TSC267 mutation, TSC268 mutation, TSC269 mutation, TSC270 mutation, TSC271 mutation, TSC272 mutation, TSC273 mutation, TSC274 mutation, TSC275 mutation, TSC276 mutation, TSC277 mutation, TSC278 mutation, TSC279 mutation, TSC280 mutation, TSC281 mutation, TSC282 mutation, TSC283 mutation, TSC284 mutation, TSC285 mutation, TSC286 mutation, TSC287 mutation, TSC288 mutation, TSC289 mutation, TSC290 mutation, TSC291 mutation, TSC292 mutation, TSC293 mutation, TSC294 mutation, TSC295 mutation, TSC296 mutation, TSC297 mutation, TSC298 mutation, TSC299 mutation, TSC300 mutation, TSC301 mutation, TSC302 mutation, TSC303 mutation, TSC304 mutation, TSC305 mutation, TSC306 mutation, TSC307 mutation, TSC308 mutation, TSC309 mutation, TSC310 mutation, TSC311 mutation, TSC312 mutation, TSC313 mutation, TSC314 mutation, TSC315 mutation, TSC316 mutation, TSC317 mutation, TSC318 mutation, TSC319 mutation, TSC320 mutation, TSC321 mutation, TSC322 mutation, TSC323 mutation, TSC324 mutation, TSC325 mutation, TSC326 mutation, TSC327 mutation, TSC328 mutation, TSC329 mutation, TSC330 mutation, TSC331 mutation, TSC332 mutation, TSC333 mutation, TSC334 mutation, TSC335 mutation, TSC336 mutation, TSC337 mutation, TSC338 mutation, TSC339 mutation, TSC340 mutation, TSC341 mutation, TSC342 mutation, TSC343 mutation, TSC344 mutation, TSC345 mutation, TSC346 mutation, TSC347 mutation, TSC348 mutation, TSC349 mutation, TSC350 mutation, TSC351 mutation, TSC352 mutation, TSC353 mutation, TSC354 mutation, TSC355 mutation, TSC356 mutation, TSC357 mutation, TSC358 mutation, TSC359 mutation, TSC360 mutation, TSC361 mutation, TSC362 mutation, TSC363 mutation, TSC364 mutation, TSC365 mutation, TSC366 mutation, TSC367 mutation, TSC368 mutation, TSC369 mutation, TSC370 mutation, TSC371 mutation, TSC372 mutation, TSC373 mutation, TSC374 mutation, TSC375 mutation, TSC376 mutation, TSC377 mutation, TSC378 mutation, TSC379 mutation, TSC380 mutation, TSC381 mutation, TSC382 mutation, TSC383 mutation, TSC384 mutation, TSC385 mutation, TSC386 mutation, TSC387 mutation, TSC388 mutation, TSC389 mutation, TSC390 mutation, TSC391 mutation, TSC392 mutation, TSC393 mutation, TSC394 mutation, TSC395 mutation, TSC396 mutation, TSC397 mutation, TSC398 mutation, TSC399 mutation, TSC400 mutation, TSC401 mutation, TSC402 mutation, TSC403 mutation, TSC404 mutation, TSC405 mutation, TSC406 mutation, TSC407 mutation, TSC408 mutation, TSC409 mutation, TSC410 mutation, TSC411 mutation, TSC412 mutation, TSC413 mutation, TSC414 mutation, TSC415 mutation, TSC416 mutation, TSC417 mutation, TSC418 mutation, TSC419 mutation, TSC420 mutation, TSC421 mutation, TSC422 mutation, TSC423 mutation, TSC424 mutation, TSC425 mutation, TSC426 mutation, TSC427 mutation, TSC428 mutation, TSC429 mutation, TSC430 mutation, TSC431 mutation, TSC432 mutation, TSC433 mutation, TSC434 mutation, TSC435 mutation, TSC436 mutation, TSC437 mutation, TSC438 mutation, TSC439 mutation, TSC440 mutation, TSC441 mutation, TSC442 mutation, TSC443 mutation, TSC444 mutation, TSC445 mutation, TSC446 mutation, TSC447 mutation, TSC448 mutation, TSC449 mutation, TSC450 mutation, TSC451 mutation, TSC452 mutation, TSC453 mutation, TSC454 mutation, TSC455 mutation, TSC456 mutation, TSC457 mutation, TSC458 mutation, TSC459 mutation, TSC460 mutation, TSC461 mutation, TSC462 mutation, TSC463 mutation, TSC464 mutation, TSC465 mutation, TSC466 mutation, TSC467 mutation, TSC468 mutation, TSC469 mutation, TSC470 mutation, TSC471 mutation, TSC472 mutation, TSC473 mutation, TSC474 mutation, TSC475 mutation, TSC476 mutation, TSC477 mutation, TSC478 mutation, TSC479 mutation, TSC480 mutation, TSC481 mutation, TSC482 mutation, TSC483 mutation, TSC484 mutation, TSC485 mutation, TSC486 mutation, TSC487 mutation, TSC488 mutation, TSC489 mutation, TSC490 mutation, TSC491 mutation, TSC492 mutation, TSC493 mutation, TSC494 mutation, TSC495 mutation, TSC496 mutation, TSC497 mutation, TSC498 mutation, TSC499 mutation, TSC500 mutation, TSC501 mutation, TSC502 mutation, TSC503 mutation, TSC504 mutation, TSC505 mutation, TSC506 mutation, TSC507 mutation, TSC508 mutation, TSC509 mutation, TSC510 mutation, TSC511 mutation, TSC512 mutation, TSC513 mutation, TSC514 mutation, TSC515 mutation, TSC516 mutation, TSC517 mutation, TSC518 mutation, TSC519 mutation, TSC520 mutation, TSC521 mutation, TSC522 mutation, TSC523 mutation, TSC524 mutation, TSC525 mutation, TSC526 mutation, TSC527 mutation, TSC528 mutation, TSC529 mutation, TSC530 mutation, TSC531 mutation, TSC532 mutation, TSC533 mutation, TSC534 mutation, TSC535 mutation, TSC536 mutation, TSC537 mutation, TSC538 mutation, TSC539 mutation, TSC540 mutation, TSC541 mutation, TSC542 mutation, TSC543 mutation, TSC544 mutation, TSC545 mutation, TSC546 mutation, TSC547 mutation, TSC548 mutation, TSC549 mutation, TSC550 mutation, TSC551 mutation, TSC552 mutation, TSC553 mutation, TSC554 mutation, TSC555 mutation, TSC556 mutation, TSC557 mutation, TSC558 mutation, TSC559 mutation, TSC560 mutation, TSC561 mutation, TSC562 mutation, TSC563 mutation, TSC564 mutation, TSC565 mutation, TSC566 mutation, TSC567 mutation, TSC568 mutation, TSC569 mutation, TSC570 mutation, TSC571 mutation, TSC572 mutation, TSC573 mutation, TSC574 mutation, TSC575 mutation, TSC576 mutation, TSC577 mutation, TSC578 mutation, TSC579 mutation, TSC580 mutation, TSC581 mutation, TSC582 mutation, TSC583 mutation, TSC584 mutation, TSC585 mutation, TSC586 mutation, TSC587 mutation, TSC588 mutation, TSC589 mutation, TSC590 mutation, TSC591 mutation, TSC592 mutation, TSC593 mutation, TSC594 mutation, TSC595 mutation, TSC596 mutation, TSC597 mutation, TSC598 mutation, TSC599 mutation, TSC600 mutation, TSC601 mutation, TSC602 mutation, TSC603 mutation, TSC604 mutation, TSC605 mutation, TSC606 mutation, TSC607 mutation, TSC608 mutation, TSC609 mutation, TSC610 mutation, TSC611 mutation, TSC612 mutation, TSC613 mutation, TSC614 mutation, TSC615 mutation, TSC616 mutation, TSC617 mutation, TSC618 mutation, TSC619 mutation, TSC620 mutation, TSC621 mutation, TSC622 mutation, TSC623 mutation, TSC624 mutation, TSC625 mutation, TSC626 mutation, TSC627 mutation, TSC628 mutation, TSC629 mutation, TSC630 mutation, TSC631 mutation, TSC632 mutation, TSC633 mutation, TSC634 mutation, TSC635 mutation, TSC636 mutation, TSC637 mutation, TSC638 mutation, TSC639 mutation, TSC640 mutation, TSC641 mutation, TSC642 mutation, TSC643 mutation, TSC644 mutation, TSC645 mutation, TSC646 mutation, TSC647 mutation, TSC648 mutation, TSC649 mutation, TSC650 mutation, TSC651 mutation, TSC652 mutation, TSC653 mutation, TSC654 mutation, TSC655 mutation, TSC656 mutation, TSC657 mutation, TSC658 mutation, TSC659 mutation, TSC660 mutation, TSC661 mutation, TSC662 mutation, TSC663 mutation, TSC664 mutation, TSC665 mutation, TSC666 mutation, TSC667 mutation, TSC668 mutation, TSC669 mutation, TSC670 mutation, TSC671 mutation, TSC672 mutation, TSC673 mutation, TSC674 mutation, TSC675 mutation, TSC676 mutation, TSC677 mutation, TSC678 mutation, TSC679 mutation, TSC680 mutation, TSC681 mutation, TSC682 mutation, TSC683 mutation, TSC684 mutation, TSC685 mutation, TSC686 mutation, TSC687 mutation, TSC688 mutation, TSC689 mutation, TSC690 mutation, TSC691 mutation, TSC692 mutation, TSC693 mutation, TSC694 mutation, TSC695 mutation, TSC696 mutation, TSC697 mutation, TSC698 mutation, TSC699 mutation, TSC700 mutation, TSC701 mutation, TSC702 mutation, TSC703 mutation, TSC704 mutation, TSC705 mutation, TSC706 mutation, TSC707 mutation, TSC708 mutation, TSC709 mutation, TSC710 mutation, TSC711 mutation, TSC712 mutation, TSC713 mutation, TSC714 mutation, TSC715 mutation, TSC716 mutation, TSC717 mutation, TSC718 mutation, TSC719 mutation, TSC720 mutation, TSC721 mutation, TSC722 mutation, TSC723 mutation, TSC724 mutation, TSC725 mutation, TSC726 mutation, TSC727 mutation, TSC728 mutation, TSC729 mutation, TSC730 mutation, TSC731 mutation, TSC732 mutation, TSC733 mutation, TSC734 mutation, TSC735 mutation, TSC736 mutation, TSC737 mutation, TSC738 mutation, TSC739 mutation, TSC740 mutation, TSC741 mutation, TSC742 mutation, TSC743 mutation, TSC744 mutation, TSC745 mutation, TSC746 mutation, TSC747 mutation, TSC748 mutation, TSC749 mutation, TSC750 mutation, TSC751 mutation, TSC752 mutation, TSC753 mutation, TSC754 mutation, TSC755 mutation, TSC756 mutation, TSC757 mutation, TSC758 mutation, TSC759 mutation, TSC760 mutation, TSC761 mutation, TSC762 mutation, TSC763 mutation, TSC764 mutation, TSC765 mutation, TSC766 mutation, TSC767 mutation, TSC768 mutation, TSC769 mutation, TSC770 mutation, TSC771 mutation, TSC772 mutation, TSC773 mutation, TSC774 mutation, TSC775 mutation, TSC776 mutation, TSC777 mutation, TSC778 mutation, TSC779 mutation, TSC780 mutation, TSC781 mutation, TSC782 mutation, TSC783 mutation, TSC784 mutation, TSC785 mutation, TSC786 mutation, TSC787 mutation, TSC788 mutation, TSC789 mutation, TSC790 mutation, TSC791 mutation, TSC792 mutation, TSC793 mutation, TSC794 mutation, TSC795 mutation, TSC796 mutation, TSC797 mutation, TSC798 mutation, TSC799 mutation, TSC800 mutation, TSC801 mutation, TSC802 mutation, TSC803 mutation, TSC804 mutation, TSC805 mutation, TSC806 mutation, TSC807 mutation, TSC808 mutation, TSC809 mutation, TSC810 mutation, TSC811 mutation, TSC812 mutation, TSC813 mutation, TSC814 mutation, TSC815 mutation, TSC816 mutation, TSC817 mutation, TSC818 mutation, TSC819 mutation, TSC820 mutation, TSC821 mutation, TSC822 mutation, TSC823 mutation, TSC824 mutation, TSC825 mutation, TSC826 mutation, TSC827 mutation, TSC828 mutation, TSC829 mutation, TSC830 mutation, TSC831 mutation, TSC832 mutation, TSC833 mutation, TSC834 mutation, TSC835 mutation, TSC836 mutation, TSC837 mutation, TSC838 mutation, TSC839 mutation, TSC840 mutation, TSC841 mutation, TSC842 mutation, TSC843 mutation, TSC844 mutation, TSC845 mutation, TSC846 mutation, TSC847 mutation, TSC848 mutation, TSC849 mutation, TSC850 mutation, TSC851 mutation, TSC852 mutation, TSC853 mutation, TSC854 mutation, TSC855 mutation, TSC856 mutation, TSC857 mutation, TSC858 mutation, TSC859 mutation, TSC860 mutation, TSC861 mutation, TSC862 mutation, TSC863 mutation, TSC864 mutation, TSC865 mutation, TSC866 mutation, TSC867 mutation, TSC868 mutation, TSC869 mutation, TSC870 mutation, TSC871 mutation, TSC872 mutation, TSC873 mutation, TSC874 mutation, TSC875 mutation, TSC876 mutation, TSC877 mutation, TSC878 mutation, TSC879 mutation, TSC880 mutation, TSC881 mutation, TSC882 mutation, TSC883 mutation, TSC884 mutation, TSC885 mutation, TSC886 mutation, TSC887 mutation, TSC888 mutation, TSC889 mutation, TSC890 mutation, TSC891 mutation, TSC892 mutation, TSC893 mutation, TSC894 mutation, TSC895 mutation, TSC896 mutation, TSC897 mutation, TSC898 mutation, TSC899 mutation, TSC900 mutation, TSC901 mutation, TSC902 mutation, TSC903 mutation, TSC904 mutation, TSC905 mutation, TSC906 mutation, TSC907 mutation, TSC908 mutation, TSC909 mutation, TSC910 mutation, TSC911 mutation, TSC912 mutation, TSC913 mutation, TSC914 mutation, TSC915 mutation, TSC916 mutation, TSC917 mutation, TSC918 mutation, TSC919 mutation, TSC920 mutation, TSC921 mutation, TSC922 mutation, TSC923 mutation, TSC924 mutation, TSC925 mutation, TSC926 mutation, TSC927 mutation, TSC928 mutation, TSC929 mutation, TSC930 mutation, TSC931 mutation, TSC932 mutation, TSC933 mutation, TSC934 mutation, TSC935 mutation, TSC936 mutation, TSC937 mutation, TSC938 mutation, TSC939 mutation, TSC940 mutation, TSC941 mutation, TSC942 mutation, TSC943 mutation, TSC944 mutation, TSC945 mutation, TSC946 mutation, TSC947 mutation, TSC948 mutation, TSC949 mutation, TSC950 mutation, TSC951 mutation, TSC952 mutation, TSC953 mutation, TSC954 mutation, TSC955 mutation, TSC956 mutation, TSC957 mutation, TSC958 mutation, TSC959 mutation, TSC960 mutation, TSC961 mutation, TSC962 mutation, TSC963 mutation, TSC964 mutation, TSC965 mutation, TSC966 mutation, TSC967 mutation, TSC968 mutation, TSC969 mutation, TSC970 mutation, TSC971 mutation, TSC972 mutation, TSC973 mutation, TSC974 mutation, TSC975 mutation, TSC976 mutation, TSC977 mutation, TSC978 mutation, TSC979 mutation, TSC980 mutation, TSC981 mutation, TSC982 mutation, TSC983 mutation, TSC984 mutation, TSC985 mutation, TSC986 mutation, TSC987 mutation, TSC988 mutation, TSC989 mutation, TSC990 mutation, TSC991 mutation, TSC992 mutation, TSC993 mutation, TSC994 mutation, TSC995 mutation, TSC996 mutation, TSC997 mutation, TSC998 mutation, TSC999 mutation, TSC1000 mutation, TSC1001 mutation, TSC1002 mutation, TSC1003 mutation, TSC1004 mutation, TSC1005 mutation, TSC1006 mutation, TSC1007 mutation, TSC1008 mutation, TSC1009 mutation, TSC1010 mutation, TSC1011 mutation, TSC1012 mutation, TSC1013 mutation, TSC1014 mutation, TSC1015 mutation, TSC1016 mutation, TSC1017 mutation, TSC1018 mutation, TSC1019 mutation, TSC1020 mutation, TSC1021 mutation, TSC1022 mutation, TSC1023 mutation, TSC1024 mutation, TSC1025 mutation, TSC1026 mutation, TSC1027 mutation, TSC1028 mutation, TSC1029 mutation, TSC1030 mutation, TSC1031 mutation, TSC1032 mutation, TSC1033 mutation, TSC1034 mutation, TSC1035 mutation, TSC1036 mutation, TSC1037 mutation, TSC1038 mutation, TSC1039 mutation, TSC1040 mutation, TSC1041 mutation, TSC1042 mutation, TSC1043 mutation, TSC1044 mutation, TSC1045 mutation, TSC1046 mutation, TSC1047 mutation, TSC1048 mutation, TSC1049 mutation, TSC1050 mutation, TSC1051 mutation, TSC1052 mutation, TSC1053 mutation, TSC1054 mutation, TSC1055 mutation, TSC1056 mutation, TSC1057 mutation, TSC1058 mutation, TSC1059 mutation, TSC1060 mutation, TSC1061 mutation, TSC1062 mutation, TSC1063 mutation, TSC1064 mutation, TSC1065 mutation, TSC1066 mutation, TSC1067 mutation, TSC1068 mutation, TSC1069 mutation, TSC1070 mutation, TSC1071 mutation, TSC1072 mutation, TSC1073 mutation, TSC1074 mutation, TSC1075 mutation, TSC1076 mutation, TSC1077 mutation, TSC1078 mutation, TSC1079 mutation, TSC1080 mutation, TSC1081 mutation, TSC1082 mutation, TSC1083 mutation, TSC1084 mutation, TSC1085 mutation, TSC1086 mutation, TSC1087 mutation, TSC1088 mutation, TSC1089 mutation, TSC1090 mutation, TSC1091 mutation, TSC1092 mutation, TSC1093 mutation, TSC1094 mutation, TSC1095 mutation, TSC1096 mutation, TSC1097 mutation, TSC1098 mutation, TSC1099 mutation, TSC1100 mutation, TSC1101 mutation, TSC1102 mutation, TSC1103 mutation, TSC1104 mutation, TSC1105 mutation, TSC1106 mutation, TSC1107 mutation, TSC1108 mutation, TSC1109 mutation, TSC1110 mutation, TSC1111 mutation, TSC1112 mutation, TSC1113 mutation, TSC1114 mutation, TSC1115 mutation, TSC1116 mutation, TSC1117 mutation, TSC1118 mutation, TSC1119 mutation, TSC1120 mutation, TSC112

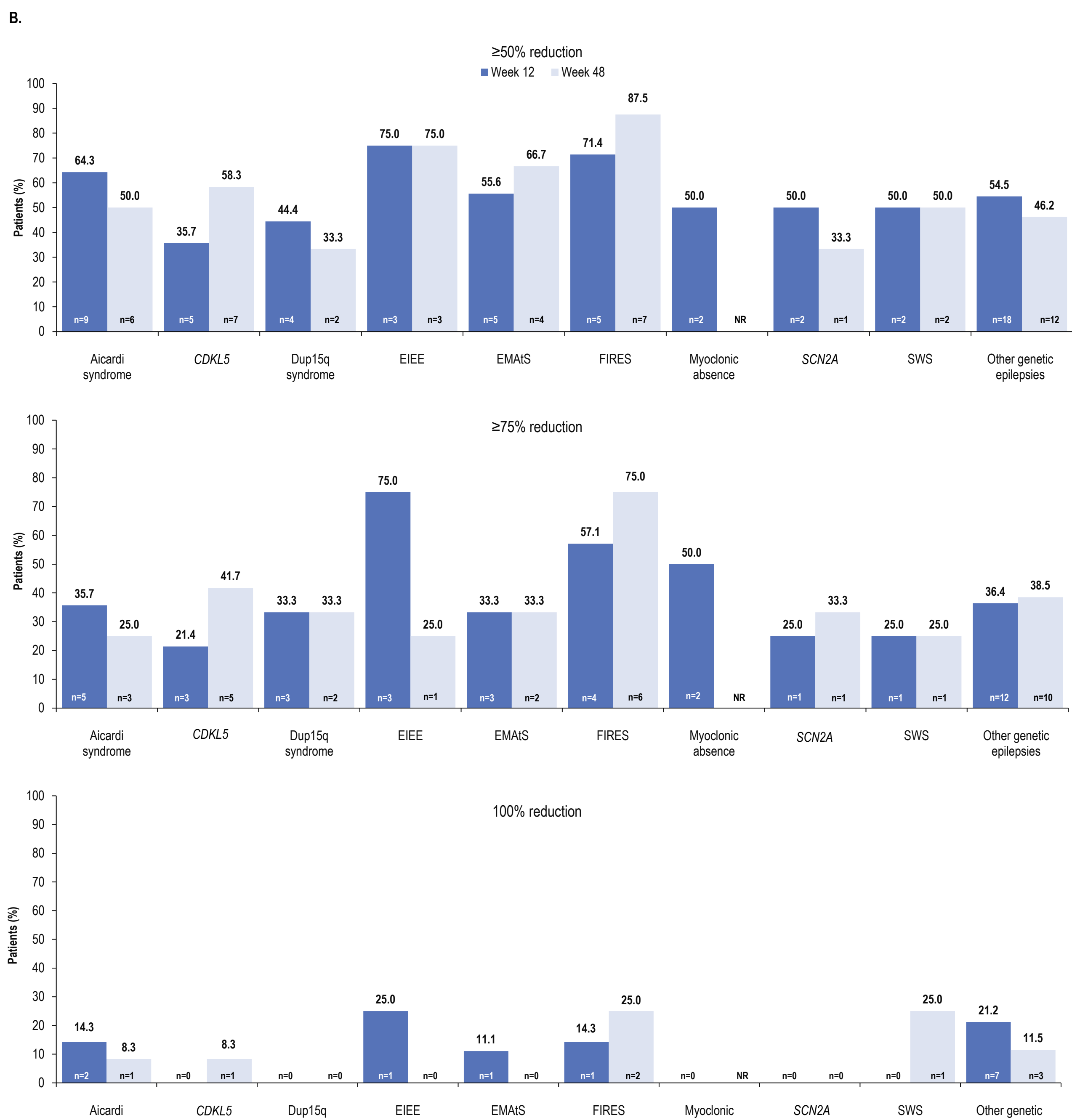
Supplementary Material

Descriptive analysis: CBD EAP effectiveness analysis set

Figure S1. Subgroup treatment response rates for convulsive seizures and total seizures: (A) convulsive and (B) total seizures at ≥50%, ≥75%, and 100%



CBD, cannabidiol; CDKL5, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAIS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; NR, not reported; SWS, Sturge-Weber syndrome.



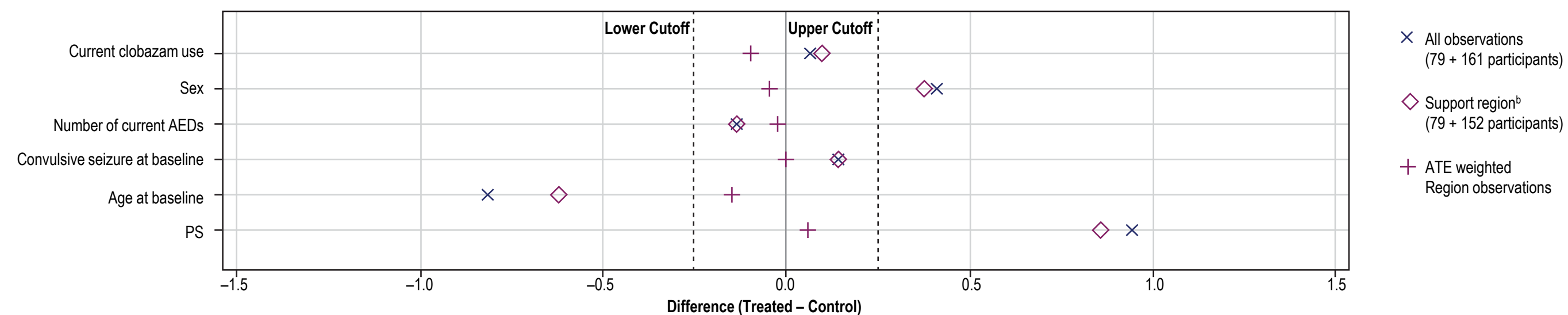
Comparative effectiveness analysis of CBD EAP vs ECA

Table S1. Baseline characteristics: Comparative effectiveness analysis set

	Unweighted		Weighted ^{a,b}	
	CBD EAP	ECA	CBD EAP	ECA
N, Effectiveness analysis set	79	161	79	152
Age, years				
Mean (SD)	9.2 (4.7)	15.3 (9.5)	11.1 (8.3)	12.2 (8.9)
Sex, female, n (%)	52 (65.8)	74 (46.0)	52 (51.2)	72 (53.3)
Number of ASMs, mean (SD)	2.8 (1.2)	2.9 (0.9)	2.9 (2.0)	2.9 (1.2)
ASMs, n (%)				
Clobazam	36 (45.6)	79 (49.1)	36 (55.0)	77 (50.3)
Levetiracetam	27 (34.2)	58 (36.0)	27 (30.1)	56 (37.2)
Valproic acid	23 (29.1)	63 (39.1)	23 (32.7)	60 (38.3)
Lamotrigine	18 (22.8)	56 (34.8)	18 (28.1)	53 (33.8)
Rufinamide	18 (22.8)	41 (25.5)	18 (27.9)	38 (23.5)
Convulsive seizure frequency, mean (SD)	328.1 (1002.1)	219.7 (409.4)	260.2 (1417.5)	260.3 (613.6)
Total seizure frequency, mean (SD)	626.9 (2187.7)	437.4 (713.5)	522.7 (3206.2)	519.1 (1003.8)

^aSummary statistics are weighted for propensity score derived by balancing the average distribution of age, sex, convulsive seizure frequency at baseline, number of concomitant ASMs, and current use of clobazam.^bTo avoid large standard error for causal effect estimates, the analysis used a support region of all observations having a percentile from 2 to 98 of the propensity score distribution. The support region included 79 CBD EAP and 152 ECA participants with balanced baseline characteristics.

ASM, antiseizure medication; CBD, cannabidiol; EAP, Expanded Access Program; ECA, external placebo control arm.

Figure S2. Standardized weighted mean difference for covariate balance assessment^a^aSummary statistics are weighted for PS derived by balancing the average distribution of age, sex, convulsive seizure frequency at baseline, number of concomitant ASMs, and current use of clobazam. Differences (SWMD) were calculated to show the difference in means of covariates between treated and control groups, standardized by the pooled SD, for each balancing covariate. A value SWMD <0.1 is acceptable; SWMD between 0.1 and 0.25 is not alarming; SWMD >0.25 denotes a serious imbalance.^bTo avoid large standard error for causal effect estimates, the analysis used a support region of all observations having a percentile from 2 to 98 of the propensity score distribution. The support region included 79 CBD EAP and 152 ECA participants with balanced baseline characteristics.

AEDs, antiepileptic drugs; ATE, average treatment difference; PS, propensity score; SWMD, standardized weight mean difference.

Safety results (CBD EAP safety analysis set)

Table S2. Summary of TEAEs reported in ≥20% of participants (CBD EAP safety analysis set)

	Overall ^a	Aicardi syndrome	CDKL5	Dup15q syndrome	EIEE	EMAIS	FIRES	SCN2A	SWS	Other genetic epilepsies
TEAEs reported in ≥20% of participants in any group by preferred term, n (%)										
Diarrhea, n (%)	44 (28.2)	7 (36.8)	7 (30.4)	2 (18.2)	3 (50.0)	3 (27.3)	5 (25.0)	0	1 (16.7)	16 (32.0)
Convulsion, n (%)	42 (26.9)	5 (26.3)	7 (30.4)	4 (36.4)	3 (50.0)	2 (18.2)	5 (25.0)	0	5 (83.3)	11 (22.0)
URTI, n (%)	29 (18.6)	3 (15.8)	6 (26.1)	0	2 (33.3)	3 (27.3)	0	0	5 (83.3)	10 (20.0)
Vomiting, n (%)	25 (16.0)	3 (15.8)	8 (34.8)	1 (9.1)	2 (33.3)	2 (18.2)	4 (20.0)	0	2 (33.3)	3 (6.0)
Pyrexia, n (%)	24 (15.4)	3 (15.8)	7 (30.4)	0	3 (50.0)	1 (9.1)	2 (10.0)	1 (20.0)	1 (16.7)	6 (12.0)
Fatigue, n (%)	22 (14.1)	4 (21.1)	6 (26.1)	3 (27.3)	1 (16.7)	2 (18.2)	1 (5.0)	0	1 (16.7)	4 (8.0)
Somnolence, n (%)	20 (12.8)	3 (15.8)	3 (13.0)	3 (27.3)	1 (16.7)	4 (36.4)	0	0	0	6 (12.0)
Pneumonia, n (%)	19 (12.2)	4 (21.1)	2 (8.7)	1 (9.1)	3 (50.0)	0	4 (20.0)	0	1 (16.7)	4 (8.0)
Status epilepticus, n (%)	17 (10.9)	3 (15.8)	1 (4.3)	1 (9.1)	1 (16.7)	1 (9.1)	1 (5.0)	1 (20.0)	1 (16.7)	7 (14.0)
Decreased appetite, n (%)	16 (10.3)	1 (5.3)	5 (21.7)	4 (36.4)	0	1 (9.1)	1 (5.0)	0	1 (16.7)	3 (6.0)
Gastroenteritis viral, n (%)	12 (7.7)	1 (5.3)	0	0	0	0	1 (5.0)	3 (60.0)	2 (33.3)	5 (10.0)
Abnormal behavior, n (%)	12 (7.7)	2 (10.5)	2 (8.7)	1 (9.1)	0	1 (9.1)	0	1 (20.0)	4 (66.7)	1 (2.0)
Sedation, n (%)	12 (7.7)	3 (15.8)	0	0	1 (16.7)	0	0	1 (20.0)	0	7 (14.0)
Rash, n (%)	12 (7.7)	0	4 (17.4)	2 (18.2)	0	1 (9.1)	0	0	2 (33.3)	3 (6.0)
Weight decreased, n (%)	9 (5.8)	3 (15.8)	2 (8.7)	1 (9.1)	0	0	1 (5.0)	1 (20.0)	0	1 (2.0)
Hypoxia, n (%)	6 (3.8)	0	1 (4.3)	0	1 (16.7)	0	1 (5.0)	1 (20.0)	0	2 (4.0)
Weight increased, n (%)	5 (3.2)	2 (10.5)	0	0	0	0	0	1 (20.0)	1 (16.7)	1 (2.0)
Ataxia, n (%)	4 (2.6)	0	0	3 (27.3)	0	0	0	0	0	1 (2.0)
Secretion discharge, n (%)	4 (2.6)	1 (5.3)	0	0	2 (33.3)	0	1 (5.0)	0	0	0
Headache, n (%)	4 (2.6)	0	0	0	0	0	0	0	2 (33.3)	2 (4.0)
Leukocytosis, n (%)	2 (1.3)	0	0	0	0	0	0	1 (20.0)	0	1 (2.0)
Pneumonia streptococcal, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Infectious mononucleosis, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Dermatitis allergic, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Pneumothorax spontaneous, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Throat irritation, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0

^aAdverse event data was not available for the participants with myoclonic absence epilepsy (n=5; 3.2%).

CBD, cannabidiol; CDKL5, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAIS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; SWS, Sturge-Weber syndrome; TEAEs, treatment-emergent adverse events; URTI, upper respiratory tract infection.

Acknowledgments: The authors would like to thank all of the study investigators, study staff, nursing team, patients, and caregivers for their participation in this research. Writing and editorial assistance was provided to the authors by Judy Eun, PharmD, on behalf of Syneos Health, and funded by Jazz Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP) 2022 guidelines.**Support:** The study was sponsored by Jazz Pharmaceuticals, Inc.**Disclosures:** All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. YP has consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.; TG, KCS, and TBS are employees of Jazz Pharmaceuticals, Inc., and hold stock and/or stock options in the company.

EAT has consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.

Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

