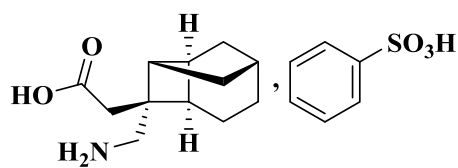


Crisugabalin Besilate Capsules

Benhuangsuan Kelijiabalin Jiaonang

2-[(1R,2R,3R,6R,8R)-2-(4-sulfamoylphenyl)-2-azabicyclo[2.2.2]oct-8-yl]acetic acid [4.2.1.0^{3,8}] -2-]



$C_{12}H_{19}NO_2 \cdot C_6H_6O_3S$

367.46

20mg $C_{12}H_{19}NO_2$

				20mg	2
					≥65
		1			40mg
2				20mg	40mg
					2
				1/2	1/4
		65			
			65		
					585
			327		
	457		6		274
	12				
				178	
40mg/	20mg bid	180			

(SOC)	(%)	
(PT)		
	82 (27.2)	96
	25 (8.3)	27
	9 (3.0)	11
	6 (2.0)	6
	3 (1.0)	3
	8 (2.7)	9
	3 (1.0)	3
	5 (1.7)	5
	4 (1.3)	4
	3 (1.0)	3
	4 (1.3)	4

0.7%

		123		40mg/
20mg bid	122	80mg/	40mg bid	3
	1%			
42.9%		29.0%		
	(%)	(%)	(%)	
	3 (2.4)	9 (7.4)	1 (0.8)	
	5 (4.1)	2 (1.6)	1 (0.8)	
	5 (4.1)	29 (23.8)	3 (2.4)	

	4 (3.3)	12 (9.8)	0
	4 (3.3)	8 (6.6)	6 (4.8)
	4 (3.3)	5 (4.1)	4 (3.2)
	3 (2.4)	3 (2.5)	0
	2 (1.6)	4 (3.3)	0
	0	5 (4.1)	0
	1 (0.8)	3 (2.5)	1 (0.8)
	3 (2.4)	2 (1.6)	0
	1 (0.8)	3 (2.5)	0
	3 (2.4)	3 (2.5)	0

		2.0%	0%	2
1	0.8%	40mg bid		
				/
	22.7%	5.7%		7.5%
0.3%	79.5%			20.5%
	5		3	
				/

4.0% 1.6% $\geq 7\%$ /

1.7% 0.8% /

1 0.6% 40mg bid

1.5% 0.3% /

6 2.0% 20mg bid 4 1.3% 40mg bid

3

2

/

18

252

65

eGFR $\geq$ 60 mL/min/1.73 m²

n=145

n=107

65

65

<65

n=448

$\geq$ 65

n=232

7.35 ~ 25.2%

CYP

CYP1A2 2B6 2C8 2C9 2C19 2D6 3A4

CYP1A

2 CYP2B6 CYP3A4

O

ATP1B1 OATP1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-K P-gp

BCRP OAT3 OCT2 P-gp BCRP OATP1B1 OAT

P1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-K OAT3 OCT2

OAT3

OCT2

4-1 4-2

PK	n=23		n=23		GMR (90%CI)
	Mean	SD	Mean	SD	
C _{max} (ng/mL)	611 (173)		721 (162)		1.20 (111.26%, 128.48%)
AUC _{0-t} (h*ng/mL)	3190 (602)		4570 (936)		1.43 (138.31%, 148.10%)
AUC _{0-∞} (h*ng/mL)	3250 (601)		4630 (931)		1.42 (137.03%, 147.50%)

PK	n=24		n=24		GMR (90%CI)
	Mean	SD	Mean	SD	
C _{max} (ng/mL)	617 (154)		687 (166)		1.12 (104.23%, 119.45%)
AUC _{0-t} (h*ng/mL)	3520 (758)		5680 (1100)		1.62 (156.66%, 167.45%)
AUC _{0-∞} (h*ng/mL)	3570 (762)		5730 (1100)		1.61 (155.91%, 166.79%)

5

PK	n=21		n=21		GMR (90%CI)
	Mean	SD	Mean	SD	
C _{max,ss} (ng/mL)	1320 (308)		1070 (269)		0.81 (76%, 87%)
AUC _{0-tau,ss} (h*ng/mL)	7350 (1100)		6190 (1430)		1.12 (79%, 87%)

:C_{max,ss}

AUC_{0-tau,ss}

0

-

_____ 5~120 mg
 1.33~1.67h
 h AUC_{0-t} T_{max} 3.96 h v.s. 1.37
 C_{max} 33.96%

0.9 400 2000 10000 ng/mL
 2.7% 2.8% 3.3%
 5~120 mg V_z/F 67~133L

CYP450

CYP CYP1A2 2B6 2C8 2C9 2C19 2D6 3A4
 CYP1A2 CYP2B6 CYP3A4
 OATP1B1 OATP1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-
 K P-gp BCRP OAT3 OCT2

2%
 5~120mg CL/F 10.6~13.8L/hr
 3.68~6.42 h

	40mg	79.21%
6.55%		
		n=606
	n=74	6.57~10.1%
	20 mg	90≤GFR<130 mL/min,
n=8	60≤GFR<90 mL/min, n=8	30≤GFR<60 mL/min
n=8	15≤GFR<30 mL/min, n=8	
C _{max}	6.00% 13.83% 21.63% AUC _{0-∞}	14.63% 119.57%
272.61%		

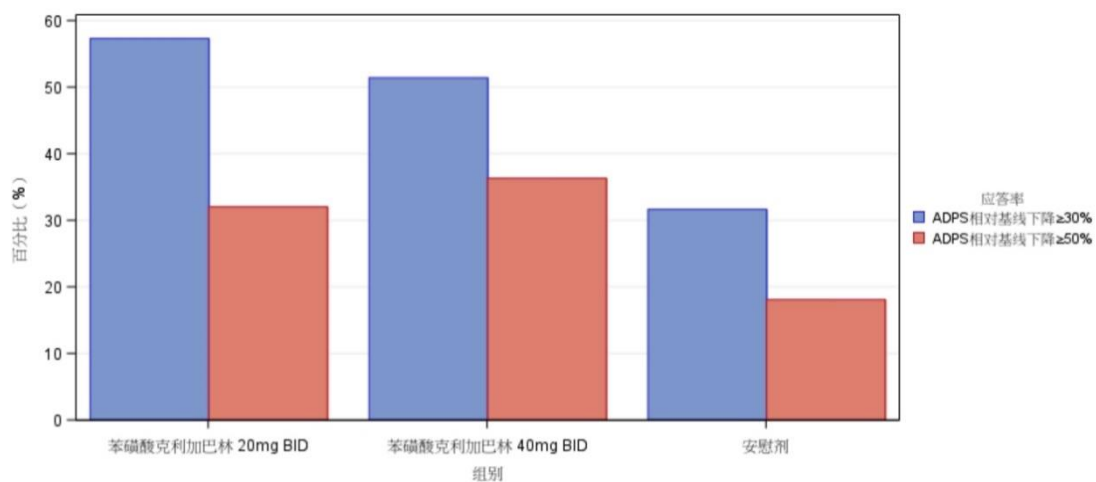
1/2 1/4

PK

PK

	18-75	
≥6	HbA1c ≤ 9.0%	30
VAS	≥ 40 mm < 90 mm	
	20mg bid 40mg bid 60mg bid 80mg bid	

	300mg/							13
	20mg bid	40mg bid						
							1:1:1	
	20mg bid	40mg bid						13
			13	ADPS				
		20mg bid	40mg bid				13	ADPS
				-2.24 (1.550)	-2.16 (1.785)	-1.23 (1.681)		
13	ADPS		≥30%				102	57.3% 92
	51.4%	56	31.6%	13	ADPS		≥50%	
	57	32.0%	65	36.3%	32	18.1%	40mg/	20mg
bid h	80mg/	40mg bid f			p<0.0001		1	2
		13	DSIS		VAS			
F								



2 13 ADPS

52 40mg bid
40mg bid
20mg bid
52 VAS
301 43
52 VAS -23.4 $\pm$ 19.38 2-
52 VAS

18 1 VAS ≥ 40 mm

1:1:1 20mg bid 40mg bid
12 12 ADPS
20mg bid 40mg bid
12 ADPS -2.338 (1.6615)
-2.513 (2.0055) -1.047 (2.0308) 40mg bid ADPS
95% CI -1.498 -1.983 -1.013 p<0.001 20mg bid
ADPS 95% CI -1.140 -1.631 -0.649

3

40mg bid

ADPS

30%

74

61.2%

66

(54.5%)

(35.5%)

12 ADPS

50%

45

(37.2%)

(38.0%)

25 (20.2%)

4

12

14

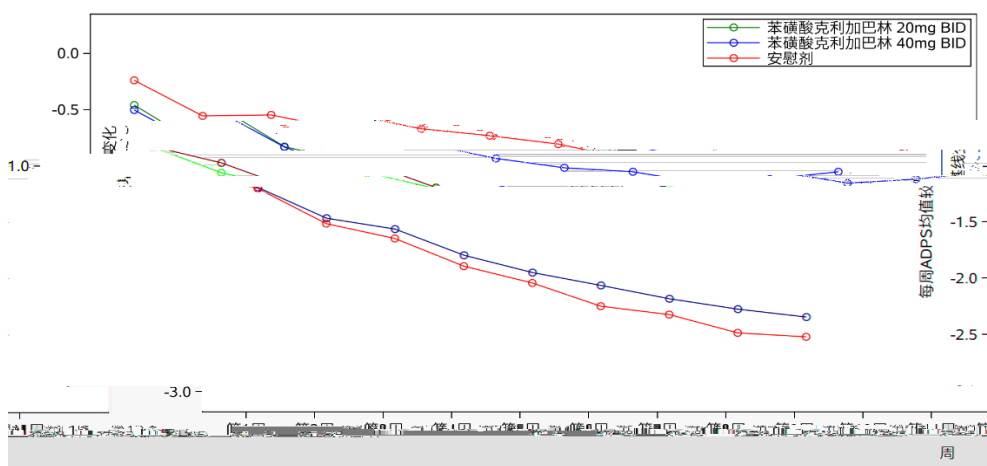
80mg/ 40mg bid

264

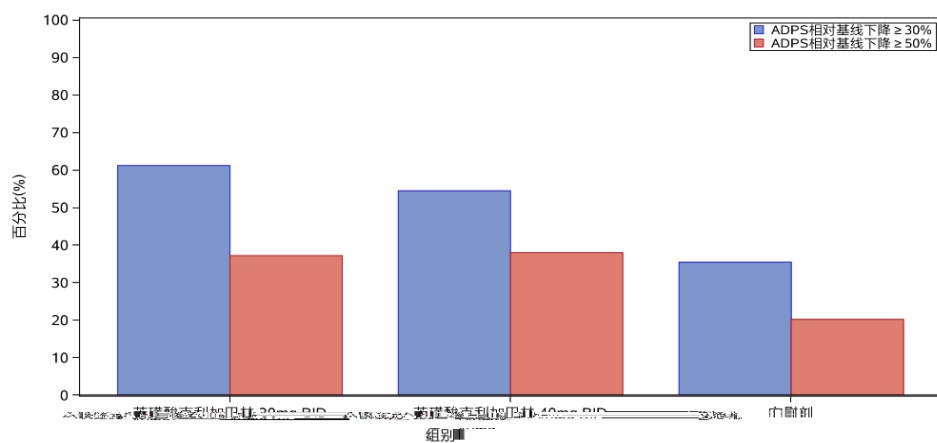
71.0%

26 VAS

-39.09 19.590



3 ADPS



4 12 ADPS

γ-	GABA	GABA _A GABA _B	
		[³ H]	
	Ames	CHL	
			4
	2	7	15 60
240mg/kg/ [		MRHD	80mg/ 1.8
7.3 29]	240mg/kg/		
		240mg/kg/	
	60 mg/kg/	240mg/kg/	
-			6~17
	5 20	100mg/kg/ 100 mg/kg/	
		-	100mg/kg/
AUC		MRHD 37	
-			6~18
	5 20	80mg/kg/ 80mg/kg/	-
			-
	20mg/kg/	AUC	MRHD 3.4
		6	21
	5 20	100mg/kg/ 100 mg/kg/	
		20mg/kg/	AUC
MRHD 5.2		100 mg/kg/	AUC
	MRHD 33		

SD 104 20 60
200 mg/kg/ 200mg/kg/ MRHD 101
140 AUC rasH2 26
6 100 400 1500 mg/kg/
1500 mg/kg/ MRHD 216 265
AUC

25

/ /

9 / 6

/

24

YBH08292024

H20240018

17

856000

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