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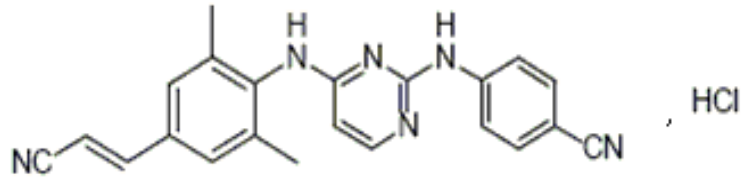
2012	12	31
2014	06	19
2015	11	12
2015	11	24
2016	05	31
2016	08	24
2016	09	20
2016	12	13
2017	07	21
2017	12	14
2019	11	19
2020	07	01

®

Rilpivirine Tablets

Lipiweilin Pian

4-[[4-[[4-[ E -2- ]-2 6- ] ]-2- ] ]



$C_{22}H_{18}N_6 \cdot HCl$

402.88(366.42+36.46)

K30

20

1

12

HIV-1 RNA

100,000

/mL 1

HIV-1

35 kg

•

HIV-1 RNA

100,000

/mL

100,000

/mL

HIV-1

RNA $\geq$ 50

/mL

25mg

12

$\geq$ 35kg

25mg

1

1

---

HIV-1 RNA 50 /mL

1 1 25 mg

1 50mg 25mg/

1 25mg

TMC278-C209(ECHO) TMC278-C215(THRIVE)

96

1368 HIV-1

686

25mg 1

104.3 104.1

48

2% 4%

10 1% 11 2%

10 1.5%

1 0.1%

1

≥2

≥2%

2

1 HIV-1

\* 2~4

96

---



2 HIV-1

1~4

96

%	DAIDS	TMC278-C209 TMC278-C215	
		+BR =686	+BR =682
1	$\geq 1.1 \sim \leq 1.3 \times \text{ULN}$	6%	1%
2	$> 1.3 \sim \leq 1.8 \times \text{ULN}$	1%	1%
3	$> 1.8 \sim \leq 3.4 \times \text{ULN}$	<1%	0
4	$> 3.4 \times \text{ULN}$	0	<1%
AST			
1	$\geq 1.25 \sim \leq 2.5 \times \text{ULN}$	16%	19%
2	$> 2.5 \sim \leq 5.0 \times \text{ULN}$	4%	7%
3	$> 5.0 \sim \leq 10.0 \times \text{ULN}$	2%	2%
4	$> 10.0 \times \text{ULN}$	1%	1%
ALT			
1	$\geq 1.25 \sim \leq 2.5 \times \text{ULN}$	18%	20%
2	$> 2.5 \sim \leq 5.0 \times \text{ULN}$	5%	7%
3	$> 5.0 \sim \leq 10.0 \times \text{ULN}$	1%	2%
4	$> 10.0 \times \text{ULN}$	1%	1%
1	$\geq 1.1 \sim \leq 1.5 \times \text{ULN}$	5%	<1%
2	$> 1.5 \sim \leq 2.5 \times \text{ULN}$	3%	1%
3	$> 2.5 \sim \leq 5.0 \times \text{ULN}$	1%	<1%
4	$> 5.0 \times \text{ULN}$	0	0
1	5.18~6.19mmol/L/200~239mg/dL	17%	31%
2	6.20~7.77mmol/L/240~300mg/dL	7%	19%
3	$> 7.77 \text{mmol/L}$ $> 300 \text{mg/dL}$	<1%	3%
LDL			



3

LDL-

HDL-

3

\*

	TMC278-C209 TMC278-C215 96							
	+BR				+BR			
		96				96		
95% CI		mg/dL	mg/dL	mg/dL		mg/dL	mg/dL	mg/dL
	546	161	166	5	507	160	187	28
HDL	545	41	46	4	505	40	51	11
LDL	543	96	98	1	503	95	109	14
	546	122	116	-6	507	130	141	11
BR= *								
96								

/

TMC278-C213

48

36 12 - &lt; 18

≥ 32 kg

HIV-1

25 mg 1

---

63.5

19 52.8% 1 2  
2 19.4%  
19.4% 13.9% 11.1% 8.3% 8.3% 5.6%  
5.6%

TMC278-C213 48

1.59 0.24 2.93 µg/dL

30 250µg ACTH 6 20%

< 18.1 µg/dL 3 48

250 µg

ACTH

DRESS

4

CYP3A

pH

(NNRTIs)



		CYP3A
		pH

60 400mg 1  
 24 13 25mg 1  
 QTcF QTcF 95%  
 2.0 5.0  
 75mg 1 300mg 1 3 12  
 QTcF 95%  
 10.7 15.3 23.3 28.4 75mg 1 300mg 1  
 C<sub>max</sub> 25mg 1 C<sub>max</sub> 2.6 6.7

DRESS

3% ≥2  
 4 1 2  
 4 6



---

75 mg 1 300 mg 1 3 12  
QTc

5

/

-

Child-Pugh A Child-Pugh B  
Child-Pugh C

HIV-1		APR		HIV-1 RNA		MACDP	
15	70	247	390	1	50	12	10
	63	2.7%	1.2%	1	50	12	10
AUC		95%CI		/mL		95%CI	
AUC		/		0.3%-3.5%		1.4%	
1		25mg		1		1	
HIV-1		HIV-1		HIV-1 RNA		MACDP	
C <sub>0h</sub>		AUC		6-12		6-12	
>99%		1		6		25	
83.3%		6-12		30-40%		12	
2		1		9		10	
0.2%		5.0%		75%		6-12	
10		10		10		10	

---

1

16

HIV-1

10

HIV-

6

17

6

19

40 120 400 mg/kg/

5 10 20 mg/kg/

-

25 mg

15

70

400 mg/kg/

HIV

HIV

1 HIV

HIV

2

HIV

3

---

400 mg/kg/

36 12 - < 18

≥ 32 kg

HIV-1

12

35 kg

P450(CYP)3A

CYP3A

CYP3A

NNRTIs

CYP3A

pH

NNRTIs

25mg

1

CYP

5

/

5

5

	↔ 2 4	pH 2                      4
	↓	
	↓	

*		CYP3A 25mg 50mg 25mg
*		CYP3A
H2 *	↔ 12 4 2	H2 pH 12 4 H2
<b>HIV- NRTIs</b>		
*	↔ ↔	2 4
<b>HIV- NNRTIs</b>		
NNRTI NNRTIs	↔ ↔ NNRTIs	NNRTIs
<b>HIV PIs</b>		
/ *	↔	/ CYP3A

		/
/ *	↔	/ CYP3A /
PIs / / / /	↔ PI	PIs CYP3A PIs
PIs	↔ PI	PIs CYP3A PIs
	↔ ↔ ↔	CYP3A
*	R - S +	
:		
= = ↔ = *		
	25mg 1	



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NRTIs

QT

QTc  
75 mg 1 300 mg 3  
12 QTc

[ ECG QT ]

TMC278-C209(ECHO) TMC278-C215(THRIVE) 48 96  
HIV-1 HIV-1 RNA $\geq$ 5000  
/mL N(t)RTI NNRTI  
RASs BR TMC278-C209  
BR N(t)RTIs TMC278-C215 BR  
N(t)RTIs  
TMC278-C215  
N(t)RTI BR

TMC278-C209 TMC278-C215

6

**6 TMC278-C209 TMC278-C215 HIV-1**

	<b>TMC278-C209</b>	<b>TMC278-C215</b>
	<b>+BR =686</b>	<b>+BR =682</b>
	36 18~78	36 19~69
	76%	76%
	24%	24%
	61%	60%
/	24%	23%
	11%	14%
	2%	2%
	1%	1%
HIV-1 RNA log <sub>10</sub> /mL	5.0 2~7	5.0 3~7
≤100,000	54%	48%
>100,000 ≤500,000	36%	40%
>500,000	10%	12%
CD4+ /mm <sup>3</sup>	249 1~888	260 1~1137
/	7%	10%
	80%	80%
	15%	15%
	5%	5%
BR=		

7 25mg 1 96 96

48 HIV-1 RNA CD4+ 200

/mm<sup>3</sup> EDURANT CD4+ 200 /mm<sup>3</sup>

EDURANT

7 TMC278-C209 TMC278-C215 96

	+BR =686	+BR =682
HIV-1RNA <50 /mL*	76%	77%
HIV-1RNA 50 /mL	16%	10%
96		
‡	4%	8%
HIV-1RNA <50 /mL	4%	5%
	<1%	<1%
HIV-1RNA <50 /mL HIV-1 RNA /mL		
≤100,000	82%	78%
>100,000	70%	75%
HIV-1RNA 50 /mL HIV-1 RNA /mL		
≤100,000	9%	8%
>100,000	24%	11%
HIV-1RNA <50 /mL CD4+ /mm <sup>3</sup>		
<200	68%	74%
≥200	81%	77%
HIV-1RNA 50 /mL CD4+ /mm <sup>3</sup>		
<200	27%	10%
≥200	10%	9%
BR=		
*CI=	95% CI -0.2 -4.7 4.3 96	
96	≥50 /mL	≥50 /mL
‡	96	

96	90-103
----	--------

TMC278-C209      TMC278-C215      96  
 CD4+      228 /mm<sup>3</sup>      219 /mm<sup>3</sup>  
 TMC278-C204      HIV-1  
 b      96      [  
 ]      96      3  
                                  25mg      1  
 600mg      1      BR      BR      N(t)RTIs  
  
 TMC278-C204      368      HIV-1-      HIV-  
 1 RNA ≥ 5000 /mL      ≤ 2      N(t)RTI  
                                  NNRTIs      N (t)RTI      NNRTI      RASs  
 96      25mg      = 93  
 = 89 HIV-1 RNA < 50 /mL      76%      71%      25 mg      CD4+  
                                  146 /mm<sup>3</sup>      160 /mm<sup>3</sup>  
 240      57%      51/89      25mg      1  
 HIV-1 RNA < 50 /mL      60%      56/93  
  
**12 - < 18**  
                                  12 - < 18      ≥ 32 kg      HIV-1  
                                  TMC278-C213      25 mg  
 2      NRTI      BR  
                                  36      48      36      14.5  
 12-17      55.6%      88.9%      11.1%  
                                  75%      28/36      HIV RNA < 100,000 /mL      28  
                                  HIV-1 RNA      44,250 /mL      2,060-92,600 /mL  
 CD4+      445.5 /mm<sup>3</sup>      123-983 /mm<sup>3</sup>

48	HIV RNA $\leq$ 100,000 /mL		>100,000 /mL	79%	
22/28	50%	4/8	HIV-1 RNA $<$ 50 /mL	$\leq$ 100,000 /mL	$>$ 100,000 /mL
			21.4% 6/28	37.5% 3/8	48 CD4+
			201.2 /mm <sup>3</sup>		

		1		(HIV-1)	
(NNRTI)		HIV-1		(RT)	HIV-1
DNA		$\alpha, \beta$	$\gamma$		
T				HIV-1	
HIV-1 <sub>IMB</sub>	EC <sub>50</sub>	0.73nM	0.27ng/mL		HIV-2
		EC <sub>50</sub>	5220nM	2510	10830nM 920
3970ng/mL					
	M	HIV-1	A B C D F G H		
EC <sub>50</sub>		0.07	1.01nM 0.03	0.37ng/mL	O
EC <sub>50</sub>		2.88	8.45nM 1.06	3.10ng/mL	
				NNRTIs	
N(t)RTIs					
PIs					
			CCR5		
		HIV-1	NNRTI	HIV-1	
-					L100I

K101E V106I A V108I E138K G Q R V179F I Y181C I V189I G190E  
 H221Y F227C M230I L

C209 C215 96

58% 57/98

/

45% 25/56

52% 51/98

/

23% 13/56

NNRTI

V90I

K101E/P/T E138K/A/Q/G V179I/L Y181C/I V189I H221Y F227C/L M230L

2.6~621 E138K

M184I

M184I V NRTI

K65R/N A62V D67N/G K70E Y115F

T215S/T K219E/R

8

>100,000 /mL

NNRTI NRTI

≤100,000 /mL

NNRTI

74% 40/54 26% 14/54 NRTI

78% 39/50

22% 11/50

/

M184I/V 77% 36/47 23% 11/47 K65R/N 100% 8/8 0% 0/8

CD4+ <200 /mm<sup>3</sup>

NNRTI NRTI

CD4+ ≥200 /mm<sup>3</sup>

NNRTI 63% 34/54 37% 20/54 NRTI

72% 36/50 28% 14/50

**8 TMC278-C209 TMC278-C215 96**

a

	<b>C209</b>	<b>C215</b>	<b>=1368</b>
	<b>+ BR</b>		<b>EFV + BR</b>

	<b>=686</b>	<b>=682</b>
	15% (98/652)	9% (56/604)
	87	43
<b>NNRTI</b> <sup>b</sup>		
	62% (54/87)	53% (23/43)
V90I	13% (11/87)	2% (1/43)
K101E/P/T/Q	20% (17/87)	9% (4/43)
K103N	1% (1/87)	40% (17/43)
E138K/A/Q/G	40% (35/87)	2% (1/43)
E138K+M184I <sup>c</sup>	25% (22/87)	0
V179I/L/D	6% (5/87)	7% (3/43)
Y181C/I/S	10% (9/87)	2% (1/43)
V189I	8% (7/87)	2% (1/43)
H221Y	9% (8/87)	0
<b>NRTI</b> <sup>d</sup>		
	57% (50/87)	30% (13/43)
M184I/V	54% (47/87)	26% (11/43)
K65R/N	9% (8/87)	5% (2/43)
A62V, D67N/G, K70E, Y115F, T215S/T K219E/R <sup>e</sup>	21% (18/87)	2% (1/43)
BR= a b V90 L100 K101 K103 V106 V108 E138 V179 Y181 Y188 V189 G190 H221 P225 F227 M230 c NNRTI NRTI E138K d A62V K65R/N D67N/G K70E L74I V75I Y115F M184I/V L210F T215S/T K219E/R e M184V/I K65R/N A62V n=3 D67N/G n=3 K70E n=4 Y115F n=2 T215S/T n=1 K219E/R n=8		

**NNRTI**

	<b>NNRTIs</b>	<b>NNRTI</b>	<b>K101P</b>	<b>Y181I</b>
Y181V	52	15	12	E138K
2.8	E138K	M184I	6.7	K103N
		K103N	L100I	

7 2 3 NNRTI 38%  
 66% 3.7~554  
 HIV-1

K101E K101P E138A E138G E138K E138R E138Q V179L  
 Y181C Y181I Y181V H221Y F227C M230I M230L

TMC278-C209 TMC278-C215 96  
 87 50 57%  
 $\geq 2.5$  86% n= 43/50  $\geq 3.3$  90% n=  
 45/50  $\geq 3.2$  62% n= 31/50  $\geq 6$   
 21 3 14%  
 95% n= 20/21

NNRTI

NNRTI

NNRTIs

Ames

400mg/kg/

25mg 1

40

(NOAEL)

25mg 1 15 70

104

20 60

160mg/kg/

40 200 500 1500mg/kg/



---

AUC

25mg      1

21                      3

HIV-1

HIV-1

**9 HIV-1**

**25mg**

**96**

	<b>25mg</b>	<b>=679</b>
AUC <sub>24h</sub> ng*h/mL		
	2235	851
	2096	198~7307
C <sub>0h</sub> ng/mL		
	79	35
	73	2~288

4~5

533 kcal

928 kcal

40%

50%

99.7%

P450(CYP)3A

50 <sup>14</sup>C-  
 85% 6.1%  
 25% < 1%

25 mg

C<sub>0h</sub> AUC<sub>24h</sub> 30-40% 10

III

-

>99%

10:

RPV 25 mg

q.d.

RPV

(SD, t <sub>max</sub> : [ ])	(6-12 ) (n=11)	(n=15)	(n=13)
C <sub>0h</sub> , ng/mL	111 69.2	65.0 23.9	63.5 26.2
C <sub>min</sub> , ng/mL	84.0 58.8	54.3 25.8	52.9 24.4
C <sub>max</sub> , ng/mL	167 101	121 45.9	123 47.5
t <sub>max</sub> , h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC <sub>24h</sub> , ng.h/mL	2714 1535	1792 711	1762 662

12 - < 18

HIV-1

25 mg

HIV-1

25 mg

C213

33~93 kg

11 12 - < 18

HIV-1

25 mg

48

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AUC <sub>24h</sub> ng•h/mL	
±	2424 ± 1024
	2269 417-5166
C <sub>0h</sub> ng/mL	
±	85 ± 40
	79 7-202

12

35 kg

8 8 8 Child-Pugh B 47% Child-Pugh C 5% Child-Pugh A 8

HIV-1 HIV-1 HIV-1

/

/

P450(CYP)3A

CYP3A

CYP3A

NNRTIs

CYP3A

pH

NNRTIs

25 mg 1

CYP

12

C<sub>max</sub> AUC C<sub>min</sub>

13

C<sub>max</sub> AUC

C<sub>min</sub>

12

		/		/		90%CI =1.00	
				C <sub>max</sub>	AUC	C <sub>min</sub>	
<b>PIs</b>							
/	800/100mg q.d.	150mg q.d.	14	1.79 1.56~2.06	2.30 1.98~2.67	2.78 2.39~3.24	
/ ( )	400/100mg b.i.d.	150mg q.d.	15	1.29 1.18~1.40	1.52 1.36~1.70	1.74 1.46~2.08	
<b>NRTIs/N[t]RTIs</b>							
	400mg q.d. 2	150mg q.d.	21	1.00 0.90~1.10	1.00 0.95~1.06	1.00 0.92~1.09	
	300mg q.d.	150mg q.d.	16	0.96 0.81~1.13	1.01 0.87~1.18	0.99 0.83~1.16	
<b>HIV</b>							
	400 mg b.i.d.	25 mg q.d.	23	1.12 1.04~1.20	1.12 1.05~1.19	1.03 0.96~1.12	

	150 mg q.d.	25 mg q.d.	23	1.04 (0.95~1.13)	1.12 (1.05~1.19)	1.25 (1.16~1.35)
	500mg	150mg q.d.	16	1.09 1.01~1.18	1.16 1.10~1.22	1.26 1.16~1.38
	40mg q.d.	150mg q.d.	16	0.91 0.79~1.06	0.90 0.81~0.99	0.90 0.84~0.96
	500mg  2	150mg q.d.	16	1.17 1.08~1.27	1.25 1.16~1.35	1.18 1.09~1.28
/	0.035mg q.d./1mg q.d.	25mg q.d.	15	< >*	< >*	< >*
	40mg  12	150mg	24	0.99 0.84~1.16	0.91 0.78~1.07	N.A.
	40mg  2	150mg	23	0.15 0.12~0.19	0.24 0.20~0.28	N.A.
	40mg  4	150mg	24	1.21 1.06~1.39	1.13 1.01~1.27	N.A.
	400mg q.d.	150mg q.d.	15	1.30 1.13~1.48	1.49 1.31~1.70	1.76 1.57~1.97
	60~100mg q.d.	25mg q.d.	12	< >*	< >*	< >*
	20mg q.d.	150mg q.d.	16	0.60 0.48~0.73	0.60 0.51~0.71	0.67 0.58~0.78
	300 mg q.d.	25 mg q.d.	18	0.69 0.62~0.76	0.58 0.52~0.65	

				25 mg q.d.		
	600mg q.d.	150mg q.d.	16	0.31 0.27~0.36	0.20 0.18~0.23	0.11 0.10~0.13
	50mg	75mg q.d.	16	0.92 0.85~0.99	0.98 0.92~1.05	1.04 0.98~1.09
CI=	N.A.=	< >=	q.d.=	b.i.d.=	2	
* 25mg						

13

		/		/ (90%CI) =1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b>PIs</b>						
/	800/100mg q.d.	150mg q.d.	15	0.90 0.81~1.00	0.89 0.81~0.99	0.89 0.68~1.16
/	400/100mg b.i.d.	150mg q.d.	15	0.96 0.88~1.05	0.99 0.89~1.10	0.89 0.73~1.08
( )						
<b>NRTIs/N[t]RTIs</b>						
	400mg q.d. 2	150mg q.d.	13	0.96 0.80~1.14	1.12 0.99~1.27	N.A.
	300mg q.d.	150mg q.d.	16	1.19 1.06~1.34	1.23 1.16~1.31	1.24 1.10~1.38
<b>HIV</b>						
	400 mg b.i.d.	25 mg q.d.	23	1.10 0.77~1.58	1.09 0.81~1.47	1.27 1.01~1.60
	150 mg q.d.	25 mg q.d.	21	1.10 (0.97~1.26)	1.06 (0.94~1.19)	0.96 (0.83~1.11)
	500mg	150mg q.d.	16	0.97 0.86~1.10	0.91 0.86~0.97	N.A.



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30 °C

30 / /

36

JX20120187

H20171075

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