

(19) (KR)
(12) (A)

(51) . Int. Cl.7 (11) 10-2004-0015230
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(30) 60/288,220 2001 05 02 (US)

(71) -4056 35

(72) , , .
18938 118

(74)

1

(54)

, 가 $N-$, ()

(skeletal related events)

(Page's disease),
 (TIH) , (BM) (MM) ()
 [Fleisch H 1997 Bisphosphonates clinical. Bisphosphonates in Bone Disease. From the Laboratory
 to the Patient. Eds: The Parthenon Publishing Group, New York/ London. 68-163]).
 가

MM

MM
가

[Lakkinen, Lancet 1992, 340, 1049-1052; McCloskey, B.J.Haematol., 1998, 100, 317-325; Berenson, N.Eng J.Med. 1996. Vol. 334, No.8, 488-493].
 [Hortobagyi G.N. , 가
 (Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases), Protocol 19 Aredia Breast Cancer Study Group, New England Journal of Medicine, 1996; 335: 1785-91; Kanis J.A. . (Clodronate decreases the frequency of skeletal metastases in women with breast cancer, Bone, 1996; 19: 663-7)].

(osteoblastic) ()
가

() 가
 [Silvio Adami, Cancer 1997 ; 80:1674-79]. 가
 [Boissier , Cancer Res; 57: 3890-3894; 1997],

[Brown , ASBMR 2000; Lee ,];
 [Corey , Cancer Research, 2000/2001 (Effects of Zoledronate on Prostate Cancer Cells), Cancer Research, 2000/2001 (Effects of Zoledronic Acid on Prostate Cancer in Vitro and in Vivo), Amer.Assoc.Cancer Res. 2000 10].

()
ZOMETA) (R) , (Novartis Pharma)

N- 가

N-

N- () , 가

, () , ,

N-

(i) N- ;
 (ii) N- , 가 ;

(iii)

N-
, N- , (SREs),
(SREs)

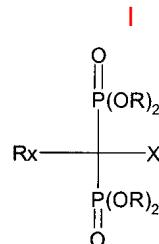
(i)

SREs N- ;

(ii) SREs N- , ,

(iii) SREs N- , , , SREs
가 .

, N- | 가



X , , , , C1-C4 ;

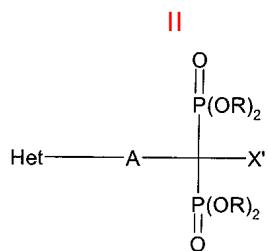
R C1-C4 ;

Rx (-)

가 , , : 3- -1- N- -1,1- (), -APD; 4- -1- (A
PD); 3-(N,N-)-1- -1,1- , -3-(), -APD; 4- -1- -
-1,1- (), -1,1- ; 1- -1,1- , -1,1- , -1,1- , -
-BP; 3-(N- -N-n-)-1- ; 6- -1- -1,1- , -1,1- , -
955); 1- -2-(-1-) -1,1- , -1,1- , -1,1- , -2-(3-)
-1,1- (), NE-10244 NE-10446; 3-[N-(2-)-N-]-1- -1,1-
- ; 1- -3-(-1-) -1,1- , -1,1- , EB 1053 (Leo); 1-(N-
-) -1,1- , FR 78844 (Fujisawa); 5- -3,4-
-2H- -3,3- , U-81581 (Upjohn); 1- -2-(

[1,2-a] -3-) -1,1- , YM529

가 . N - II



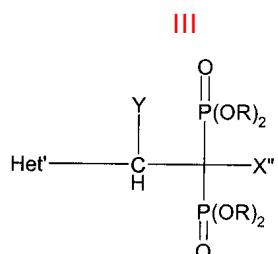
Het , , , , , , , , 1,2,3- , , 1,2,4-

A 1 8

X'

R

,
가 .



Het', , , , , , , , ,
C₁-C₁ C₁-C₁ 5-

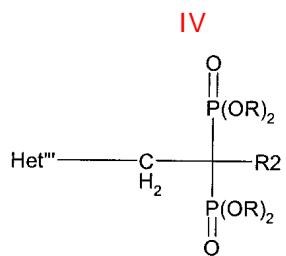
Y C₋₁ - C₋₄ :

$$X' = \{x_1, x_2, x_3, x_4, c_{-1}, c_1, c_2, c_3, c_4\}$$

R C₁ -C₄ .

, 가 .

IV



N-

N-

N-

- (Taxol), , LHRH , , (Cisplatin) ,
- / .

N -

가

가

N-

1:

() 197.3mg

52.7mg

((R) PH 105)

250.0mg

HP-M 603 10.0mg

2.0mg

8.0mg

270.0mg

(Eudragit) (R) L30D () 90.0mg

21.0mg

(Antifoam) (R) AF 2.0mg

7.0mg

390.0mg

(R) PH105

HP-M 603,

(PEG) 8000

(R) L30D,

(R) AF

(Hofliger and Krag)

() 0)

2:

1 -

- 2 - (

- 1 -) -

- 1, 1 -

:

(PIB)300 (Oppanol B1, BASF) 5.0g

PIB 35000 (B10, BASF) 3.0g

PIB 1200000 (B100, BASF) 9.0g

1 - -2- 20.0g

(Azone), , (Irvine)/CA)

20.0g

100.0g

■

, 150g (100-125 (Hostaphan), (Kalle))
 300mm 75 g/m² (60 15) , -
 (75mm, (Laufenberg)) 5 30cm²

3: 1.0mg , 1- , -2-(-1-) -1,1- (1mg/ml) .
.1ml , () .

() 1.0mg

46.0mg

3 x2H₂O 3.0mg

(3mg/ml)

19.73mg

(5.0mg)

250mg

5ml

1.

2.

2.1

가 , 14 가가 (1)
2 , 1 2 , 60 (20
1 2 . 2 가 3
6 (12)

* -		1 ()	
		가	가 1 2
1	0 21	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 2	22
-2	51 54 57	0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48	60
	3 3 3	4mg 8mg	3 3 3

-	2 ()	
	가	가
	23 24 25 26 27 28 29 30 31 32 33	34
	63 66 69 72 75 78 81 84 87 90 93	96
	3 3 3	4mg 8mg

$$* \quad \quad 2 \quad , \quad \quad -3 \quad +7$$

: 12

가 :

15 (60) 1

9 (36) 2

: 24 (96)

: 36

2.2

2.2.1

18

가 (>3) 가 , 3 가 , 1 가 ,

1 () :

2 , 3 PSA PSA
0.4ng/ml

1 , 1 가 , 1

0, 1 2 ECOG 가

1 ,
(2) ().

1 1 2 (1).

가 (50ng/ml) (1).

2 3 ().

(2) 2 ,
(2) 30 ()

가 , 가

· 3.0mg/dL (265 μ /L)

· 8.0mg/dL (2.00 /L) 11.6mg/dL (2.90 /L) ()

5

6

가

(

),

,

2.3**2.3.1**

24

3 5-

500mg

(open-label)

가

'1

'1

가

()

4mg

(4000 μ g)

8

36 46 (2 8)

5

4mg

5ml

(0.9%)

가 50ml가

(2 33),

3 50ml
1

4mg + ()

500mg

3 50ml
1

8mg + ()

500mg

3 50ml

+ ()

500mg

1

3-

		#		가	
NS I.V.	4mg, 3 2-33	4.0mg/ 5ml/ 1	5.0ml	45ml	50ml
NS I.V.	8mg, 3 2-33	4.0mg/ 5ml/ 2	10ml	40ml	50ml
,	3 NS I.V.	2-33 N/A	N/A	50ml	50ml

가	, 5-	50ml	:	8mg	가	4mg	15-	100ml
	,		,	8mg			8mg	
							4mg	

2.4

가 :

, ,
/

/

) / , , (, , (, ,
)가 - 가 (2.3.3).

/ /

3.

(N=208)	44.2%	,	4mg (N=214) (p=0.021)	8/4mg (N=221) 0.222	22.1%	33.2% 4mg	38.5% 8/4mg
13.1%	14.9%	-	,	-	-	-	-
(p=0.015)	(p=0.054)	.	4mg	-	-	-	-
, 8/4mg			363	320		(p=0.011)	0.491
4mg						.	15-

3 4mg 15- , 가

(57)

1.

N-

, 가

2.

N-

3.

N-

4.

N-

5.

N- , 가

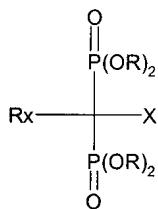
6. 가 N-

7.
N-
SREs ,

8. SREs N -

9. 1 2 N- 가 | 가

◀ ▶



$$x \in \{c_1, c_2, c_3, c_4\}$$

R C₁-C₄

Rx () - ()

10. N-가

(APP):

-3-(N,N-dimethylamino)propanoate-1,1'-Biphenyl-4-carboxylic Acid

$$4 - \dots - 1 - \dots - 1, 1 - \dots (\dots)$$

1-
-3-(
)-

-6- -1- -11- - - - -BP:

ABD (-RM 21.0955);

$$1 - 2 \left(1 - \frac{1}{\sqrt{2}} \right) = 1.1$$

1 - - 2 - (3-) - 1,1 - (), N -
N - NE-10244 NE-10446:

3-[N-(2-) -N-]-1- -1,1- ;
 1- -3-(-1-) -1,1- , EB 1053 ();
 1-(N-) -1,1- , FR 78844 ();
 5- -3,4- -2H- -3,3- , U-81581 ();
 1- -2-([1,2-a] -3-) -1,1- , YM529,
 가 .

11.

1 2 (,) N- 가 가 2-(-1-)-1-

12.

N- .