

!" #&/

4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

-\$®

(REABILEN-ECOPHARM®)

!::04:

1 <; :@0?5;L=>W4V2 =5 <5=H5 0,32 <3/<; C ?5@5@0EC=:C =0 @CB8=, 2=>28E :8A;>B =5 <5=H5 0,30 <3/<; C ?5@5@0EC=:C =0 O1;CG=C :8A;>BC) V7 B@>7G8==8: 5:AB@0:FVW: 5B0=>; 96%.

V:0@AL:0 D>@<0. □@0?;V.

\$0@<0:>B5@0?52B8G=0 3@C?0.

AB8@8. >4 ATCL03A X.

@>B82V@CA=V 70A>18 ?@O<>W 4VW. >4 ATC J05A X.

;V=VG=V E0@0:B5@8AB8:8.

>:070==O.

@5?0@0B ?>:070=89:

- 4;O ;V:C20==O ?VA;O>?5@0FV9=8E V=D5:FV9 B0 2V@CA=>-10:B5@V0;L=8E CA::04=5=L C >=:>;>3VG=8E E2>@8E;
- 4;O ;V:C20==O 2V@CA=8E V=D5:FV9 B0 2V@CA=>-10:B5@V0;L=8E CA::04=5=L, A?@8G8=5=8E V45DVF8B0<8, I> @>72820NBLAO ?V4 G0A B0 ?VA;O ?@>2545==O EV- B0 ?@><5=52>W B5@0?VW;
- C :>@N20=L, 28::8:0=8E >=:>35==8<8 2V@CA0<8 ?0?V;>8, 2V@CAV2 35@?5AC 2AVE B8?V2, 35?0B8BV2 B0 !, >?>@BC=VAB8G=8E V=D5:FV9 ?@8 .

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> :>5=BV2 ?@5?0@0BC. 8@07:0 H;C=:0 01> 420=04FOB8?0;>W :8H:8. CB>V@N20==O.

!>AV1 70AB>AC20==O B0 4>78.

@5?0@0B 4>7CTBLAO 70 4>?><>3>N :@0?5;L=8FV. 5>1EV4=C :V;L:VABL ?@5?0@0BC =0:0?0B8 C 2>4C (1-2 AB>;>2V ;>6:8), ?@89<0B8 70 10-15 E28;8= 4> W48, 0 ?@8 ;V:C20==V 2V@CA=8E 35?0B8BV2 G5@57 1,5-2 3>48=8 ?VA;O W48.

>70 V B@820;VABL ;V:C20==O 70;568BL 2V4 E0@0:B5@C ?>:070=L B0 2V:C ?0FVT=B0.

>@>A;V:

V:C20==O ?VA;O>?5@0FV9=8E V=D5:FV9 B0 2V@CA=>-10:B5@V0;L=8E CA::04=5=L C >=:>;>3VG=8EE2>@8E:

1-9 B8645=L ?> 7 :@0?5;L 2 @078 =0 45=L;  
2-3-9 B8645=L ?> 12 :@0?5;L 2 @078 =0 45=L;  
4-9 B8645=L 8 B8645=L ?> 15 :@0?5;L 2 @078 =0 45=L.  
C@A ;V:C20==O 2

V:C20==O 2V@CA=8E V=D5:FV9 B0 2V@CA=>-10:B5@V0;L=8E CA::04=5=L, A?@8G8=5=8E V45DVF8B0<8, I> @>72820NBLAO ?V4 G0A B0 ?VA;O ?@>2545==O EV- B0 ?@><5=52>W B5@0?VW:

1-9 B8645=L ?> 7 :@0?5;L 2 @078 =0 45=L;  
2-3-9 B8645=L ?> 12 :@0?5;L 2 @078 =0 45=L;  
4-3> B86=O V 2?@>4>26 12 ?> 15 :@0?5;L 2 @078 =0 45=L.  
C@A ;V:C20==O 12

# :>N ;V:C20==O 70E2>@N20=L 28::8:0=8E >=:>35==8<8 2V@CA0<8 ?0?V;<8:

1-9 B8645=L ?> 7 :@0?5;L 2 @078 =0 45=L;  
2-9, 3-9 B8645=L ?> 15 :@0?5;L 2 @078 =0 45=L;  
4-9 B8645=L ?> 12 :@0?5;L 2 @078 =0 45=L.  
"@820;VABL ;V:C20==O ?0?V;<02V@CA=>W V=D5:FVW AB0=>28BL 3

# :>N ;V:C20==O 70E2>@N20=L 28::8:0=8E 2V@CA0<8 35@?5AC 2AVE B8?V2 B0 >?>@BC=VAB8G=8E V=D5:FV9 ?@8 :

>@>A;V B0 4VB8 2V:< 2V4 12 @>:V2:  
 ?> 7 :@0?5;L 2 @078 =0 45=L ?@>BO3< =0ABC?=8E 3 4=V2;  
 ?> 10 :@0?5;L 2 @078 =0 45=L ?@>BO3< =0ABC?=8E 3 4=V2;  
 ?> 12-15 :@0?5;L 2 @078 =0 45=L.  
C@A ;V:C20==O 3

# :>N ;V:C20==O 35?0B8BV2 B0 !:

;O 4>@>A;8E B0 4VB59 2V:< AB0@H5 12 @>:V2 @5:<5=4>20=0 B0:0 AE5<0 4>7C20==O:  
 7 1-3> ?> 3-9 45=L ?> 4 :@0?;V 2 @078 =0 45=L;  
 7 4-3> ?> 6-9 45=L ?> 7 :@0?5;L 2 @078 =0 45=L;  
 7 7-3> 4=O ?> 15 :@0?5;L 2 @078 =0 45=L.  
;O ;V:C20==O 2V@CA=8E 35?0B8BV2 B0 ! C 4VB59 2V:< 4> 12 @>:V2 28:>@8AB>2CNBL 48BOGC ;V:0@AL:C D>@ A8@>? \$;02>7V4®.  
"@820;VABL ;V:C20==O =5 <5=H5 6-12

VB8:

>7C20==O ?@5?0@0BC ?@>2>48BLAO 2V4?>2V4=> 4> 2V:>28E 4>7 107>2>W AE5<8 ;V:C20==O (482. B01;.1).

# 72'O7:C 7 =0O2=VABN C ?@5?0@0BV =5<5=H5 85 % 5B0=>;C 4VBO< 4> 6 @>:V2 A;V4 @>72>48B8 4>7>20=C :V;L:VABL ?@5?0@0BC501V;5=-□  
:>D0@<® 7 FC:@>< C 50 <; >E>;>465=>W 4> :V<=0B=>W B5W 2>48.

"01;8FO 1. V:>2V 4>78 ?@5?0@0BC 501V;5=-□:>D0@<® 4;O 4VB59:

V::	>70:
VB8 4> 1 @>:C	?> 1 :@0?;V =0 45=L
VB8 2V4 1 4> 2 @>:V2	?> 1 :@0?;V 2 @078 =0 45=L
VB8 2V4 2 4> 4 @>:V2	1-9 B8645=L ?> 1 :@0?;V 2 @078 =0 45=L; 7 2-3> B86=O ?> 2 :@0?;V 2 @078 =0 45=L.
VB8 2V4 4 4> 6 @>:V2	1-9 B8645=L ?> 3 :@0?;V 2 @078 =0 45=L; 7 2-3> B86=O ?> 4 :@0?;V 2 @078 =0 45=L.
VB8 2V4 6 4> 9 @>:V2	1-9 B8645=L ?> 5 :@0?5;L 2 @078 =0 45=L; 7 2-3> B86=O ?> 9 :@0?5;L 2 @078 =0 45=L.
VB8 2V:< 2V4 9 4> 12 @>:V2	1 -9 B8645=L ?> 6 :@0?5;L 2 @078 =0 45=L; 7 2-3> B86=O ?> 10 :@0?5;L 2 @078 =0 45=L.

"@820;VABL ;V:C20==O C ?54V0B@8G=V9 ?@0:B8FVB0:0 6 O: V C 4>@>A;8E.

>2=VH=T 70AB>AC20==O:

4;O ;V:C20==O H:V@8 ?@8 2V@CA=8E B0 2V@CA=>-10:B5@V0;L=8E CA.;:04=5==OE (V=D5:FV9 ?@>AB>3> 35@?5AC H:V@8, 3>AB@8E D>@<  
>?5@V7C20;L=>3> 35@?5AC, ?0?V;<0B>7C H:V@8) ?@5?0@0B A;V4 =0=>A8B8 C 283;O4V 0?;V:0FVW =0 30-40 E28;8= 157?>A5@54=L> 7 D;0:>=0  
=0 C@065=C 4V;O=:C 01> @>7G8= ?@5?0@0BC 4> 3-5 @07V2 =0 45=L. /:I> C@065=0 A;87>20 >1>;>=:0 ?>@>6=8=8 @>B0, 28:>@8AB>2CNBL  
@>7G8= ?@5?0@0BC (4;O ?@83>BC20==O @>7G8=C =5>1EV4=> 1,5 <; (36-38 :@0?5;L) ?@5?0@0BC @>725AB8 C 10 <; DV7V>;>3VG=>3> @>7G8=C  
E;>@84C =0B@VN), O:89 CB@8BV 5-10 E28;8=, ?@>F54C@C ?>2B>@8B8 4> 3-5 @07V2 =0 45=L.

>2=VH=T 70AB>AC20==O A;V4 ?@>4>26C20B8 4> 7=8:=5==O >7=0: C@065==O H:V@8 B0 A;87>28E >1>;>=:.

@8 ?5@28==>6 ?@8 ?0?V;<02V@CA=V9 V=D5:FVW 70AB>A>2CNBL 203V=0;L=V B0=8 7 @>7G8=< ?@5?0@0BC.

;O ?@83>BC20==O @>7G8=C =5>1EV4=> 72-75 :@0?5;L ?@5?0@0BC @>725AB8 C 20 <; DV7V>;>3VG=>3> @>7G8=C E;>@84C =0B@VN. "5@  
78FVW 203V=0;L=8E B0=V2 30-40 E28;8=, ?@>2>48B8 ?@>F54C@8 2 @078 =0 45=L.  
@8 28=8:=5==V 2V4GCBBO ?>4@07=5==O C ?VE2V =5>1EV4=> 71V;LH8B8 :V;L:VABL @>7G8==8:0. >2=VH=T 70AB>AC20==O A;V4 ?@>4>26C20B8  
4> 7=8:=5==O >7=0: C@065==O H:V@8 B0 A;87>28E >1>;>=:.

>1VG=V @50:FVW.

0AB>AC20==O ?@5?0@0BC, O: ?@028;>, =5 28;;8:0T ?>1VG=>W 4VW. !?>AB5@V30;8AO ?>>48=>:V 28?04:8 H;C=:>2-:8H:>28E @>7;04V2 1V;L 2  
5?V30AB@0;L=V9 4V;O=FV, =C4>B0, 1;N20==O, 4V0@5O (?@8 =0O2=>ABV 40=8E A8EV4=> ?@89<0B8 ?@5?0@0B G5@57 1,5-2 3>48=8 ?VA;O  
W48). >6;825 B@0=78B>@=5 ?V428I5==O B5 38 ! =0 3-10-9 45=L B5@0?VW ?@5?0@0B>

;5@3VG=V @50:FVW @>72820NBLAO @V4:>, 3>;>2=8< G8=>< C 283;04V 5@8B5<0B>7=8E 28A8?0=L. # ?>>48=>:8E 28?04:0E <>6;8289 3>;>2=89  
1V;L, 7030;L=0 A;01:VABL.

# ?0FVT=BV2 7 2V@CA=8<8 35?0B8B0<8 C 10-15 % E2>@8E V7 28@065=8< F8B>;VB8G=8< A8=4@>>< A?>AB5@V30TBLAO ?V428I5==O  
0:B82=>ABV 0B@0=AD5@07 (@V4H5 @V2=O 1V;V@C1V=C).

# ?0FVT=BV2 7 E@>=VG=8< 30AB@>4C>45=VB>< <>6;825 703>AB@5==O 30AB@>4C>45=VBC, 28=8:=5==O 30AB@>57>D0350;L=>3> @5D;N:AC  
(@5D;N:A-57>D03VBC).

@8 AC20==V ?@5?0@0BC 501V;5=-□:>D0@<® <>6;820 ?>O20 2V4GCBBO ?5GV==O, A25@156C, ACE>ABV H:V@8.

5@54>7C20==O.

8?04:8 ?5@54>7C20==O =52V4>

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

@8 ?@>2545==V 4>;:V=VG=8E 4>A;V465=L B5@0B>35==>W, W, 5<1@V>B>:A8G=>W B0 :0=F5@>35==>W 4VW =5 28O2;5=>. ;V=VG=89 4>A2V4  
70AB>AC20==O ?@5?0@0BC C II B0 III B@8<5AB@0E 203VB=>ABV B0 2 ?5@V>4 3>4C20==O 3@C44N =530B82=>3> 2?;82C =5 28O282 (:;V=VG=V  
40=V ?@> 70AB>AC20==O ?@5?0@0BC C -1V2 C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

VB8.

0AB>AC20==O ?@5?0@0BC 501V;5=-□:>D0@<® 4VBO< <>6;825 2V4 =0@>465==O.

A>1;82>ABV 70AB>AC20==O.

@8 ;V:C20==V 2V@CA=8E 35?0B8BV2 C 10-15 % E2>@8E 7 28@065=8< F8B>;VB8G=8< A8=4@>>< G5@57 3-4 B86=V ?VA;O ?>G0B:C ;V:C20==O  
A?>AB5@V30TBLAO ?V428I5==O 0:B82=>ABV 0B@0=AD5@07, @V4H5 @V2=O 1V;V@C1V=C, O:5 B@820T 2?@>4>26 2 - 4-E B86=V2 B0 =5  
?>B@51CT 2V4

# ?0FVT=BV2 7 E@>=VG=8< 30AB@>4C>45=VB>< C @07V 703>AB@5==O 30AB@>4C>45=VBC ?@8 28=8:=5==V 30AB@>57>D0350;L=>3>  
@5D;N:AC =5>1EV4=> ?@89<0B8 ?@5?0@0B G5@57 1,5-2 3>48=8 ?VA;O W48.

@8 B@0=78B>@=>1EV4=> B82>, =0 2-3 4=V, 7<5=H8B8 4>7C ?@5?0@0BC 501V;5=-□:>D0@<® 242VGV.

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B× 01> @>1>BV 7 V=H8<8 <5E0=V7<0<8.

530B82=>3> 2?;82C =0 28:>=0==O ?>B5=FV9=> =5157?5G=8E 284V2 4VO;L=>ABV, O:V ?>B@51CNBL >A>1;82>W C2038 B0 H284:>W @50:FVW, =5 28O2;5=>.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

V4 G0A .;V=VG=>3> 70AB>AC20==O 2AB0=>2;5=> <>6;82VABL B0 4>FV;L=VABL :×1V=0FVW ?@5?0@0BC 501V;5=-□:>D0@<® 7 0=B81V>B8:0<8 B0 ?@>B83@81:>28<8 ?@5?0@0B0<8 4;O ;V:C20==O 2V@CA=>-10:B5@V0;L=8E V 2V@CA=>-3@81:>28E 70E2>@N20=L. 530B82=8E ?@>O2V2 C=0A;V4>: 270T<>4VW 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 =5 2AB0=>2;5=>.

82G5==O 270T<>4VW 7 V=H8<8 F8B>:V=0<8 B0 V<>4C;OB>@0<8 =5 ?@>2>48;>AL.

\$0@<0:>;>3VG=V 2;0AB82>ABV.

\$0@<0:>48=0

VO ?@5?0@0BC 501V;5=-□:>D0@<® =0 ?CE;8==89 @VAB.

@5?0@0B 501V;5=-□:>D0@<® 4VT =0 .;VB8=8 ?CE;8= F8B>AB0B8G=>.

>A;V465==O<8 =0 ?5@5I5?;N20=8E <>45;OE ?CE;8= B0 2 4>A;V40E in vitro 2AB0=>2;5=>, I> ?@5?0@0B 30;L@<0;V70FVN :V;L:VA=>3> A.;04C "-;V F8BV2 C ?5@8D5@8G=V9 :@>2V B0 ?>A8;5==O< F8B>B>:A8G=>W 0:B82=>ABV ?@8@>4=8E :V;5@V2.

# 4>A;V40E in vivo =0 5:A?5@8<5=B0;L=V9 <>45;V ?>:070=> 30;LABC <5;0=><8 16 C <8H59 70 @0EC=>: 0:B820FVW VW A8AB5<8, DC=:FVW B8=C. B@>?=0 4VO.

501V;5=-□:>D0@<® V=4C:CT A8=B57 5=4>35==8E V=B5@D5@>=V2 (\$) 2 V:>1C 0:B82=VABL \$-0;LD0 71V;LHC20;0AO 4> 23 >4<;. 2 4> 9 4V1

28O28;0AO 7ABV \$C 1V: \$-30<<0, <0:A8<0;L=89 B8B@ 287=0G02AO =0 3-9 45=L ;V:C20==O. >A;V465==O 0:B82=>ABV \$G5@57 63> ?@89>

715@565==O ?>3> ?V428I5==O @V2=O \$-0;LD0. @8 I>45==> 28O2;5=> ?@83=VG5==O 0:B82=>ABV 0;LD0 V 30<<0-\$, I> A2V4G8BL ?@>

2V4ACB=VABL @5D@0:B5@=>ABV VB@>?=8E .;VB8= 4> V=4C:FVW V=B5@D5@>=C ?@5?0@0B< 501V;5=-□:>D0@<®.

=B8>:A840=B=0 4VO.

@5?0@0B 4>7>70;56=> 30;L20=8E 2V;L=>@048:0;L=8E ?@>F5AV2, ?V428ICNG8 ABV9:VABL .;VB8= 4> 2V;L=>@048:0;L=>3> AB@5AC. >2545=in vivo, I> ?@5?0@0B 1V;LH5 =V6 C 2 @078 30;L@048:0;L=8E ?@>F5AV2, V=4C:>20=8E ?5@>:A84× 2>4=N.

>A;V465==O<8 =0 .;VB8==>2;5=>, I> ?@5?0@0B 30;L:A84@048:0;C=0=V>=C ?@0:B8G=> 4> =C;O 70 24 3>48=8 7 <><5=BC 70AB>AC20==O

?@5?0@0BC 501V;5=-□:>D0@<®, B>1B> ?V4B@8:A840=B=89 AB0BCA .;VB8=.

@>B82V@CA=0 4VO.

@5?0@0B <0T ?@OB82V@CA=C 4VN 2 H8@>:>=:>35==V 2V@CA8: 2V@CA ?0?V;>×8 ;N48=8, 2V@CAV2 35@?5AC 2AVE B8?V2, 35?0B8BV2 B0 !, - V=D5:FVW.

501V;5=-□:>D0@<® ?@83=VGCT 0:B82=VABL :0B0;VB8G=8E F5=B@V2 2V@CA>A?5F8DVG=8E D5@<5=BV2 A8=B57C (B0 -2V@CAV2). #

4>A;V465==OE in vitro B0 in vivo 4>2545=0 ?@>B82V@CA=0 0:B82=VABL O: ?@8 ?@>DV;0:B8FV, B0: V ?@8 ;V:C20==V 2V@CAV2 35@?5AC 2AVE B8?V2, 2V@CAC ?0?V;>×8, 35?0B8BV2 B0 !, .

501V;5=-□:>D0@<® C 4>A;V465==OE in vitro, in vivo ?@872>48BL 4> ?>2=>3> ?@83=VG5==O @5?@>4C:FVW 2V@CAC ?0?V;>×8 ;N48=8 B0 =>@

<0;V7CT B8G=C 0:B82=VABL V @V25=L 0=×0;L=8E 7V2.

;:>:CT =59@>3> HB0

?>?B>7CB2>@N20;L=0 4VO.

@5?0@0B T <>4C;OB>@<< 0?>?B>7C, ?V4A8;NT 4VN 0?>?B>7V=4C:CNG8E @5G>28=, I> A?@8OT 1V;LH H284:V9 5;V28E .;VB8=.  
501V;5=-□:;>D0@<® C 4>A;V465==OE in vitro, in vivo 71V;LHCT @V25=L A?>=B0==>3> B0 V=4C:>20=>3> 0?>?B>7C, 7=86CNG8 0:B82=VABL  
?@>;VD5@0B82=8E ?@>F5AV2 C ?CE;8=V. ?>?B>7>4C;NNG89 5D5:B =5 @>7?>2AN46CTBLAO =0 B8<>F8B8 B0 A?;5=>F8B8.  
?:82 =0 45B>:A8:0FV9=C DC=:FVN =8@>: B0 ?5GV=:8.

# 4>A;V465==OE in vivo 2 C<>20E E@>=VG=>3> 5:A?5@8<5=BC 1C;0 282G5=0 45B>:A8:0FV9=0 4VO ?@5?0@0BC 501V;5=-□:;>D0@<® . =0;V7 35  
<>3@0<, DC=:FV>=0;L=>3> AB0=C ?5GV=:8, =8@>: 2 C<>20E B@820;>3> 22545==O 5:7>B>:A8=V2 ?>:0702, I> 501V;5=-□:;>D0@<® ?>:@0ICT  
?>:07=8:8 45B>:A8:0FV9=>W DC=:FVW ?5GV=:8 B0 =8@>:, A?@8OT 040?B0FVW >@30=V7=5A?@8OB;828E C<>2 9>3> DC=:FV>=C20==O,  
28;;8:0=8E =0A;V4:0<8 EVB5@0?VW B0 ?@<5=52>W B5@0?VW. 024O:8 FL>A;01;NT =530B82=V =0A;V4:8 ?@<5=52>W B5@0?VW B0 EV  
B5@0?VW. >:@0ICT ?>:07=8:8 :@>2V.

\$0@<0:>:V=5B8:0. 5 282G0;0AO.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV:

@V48=0 B5<=>-75;5=>3> :>;L>@C 7V A?5F8DVG=8< 70?0E>

"5@ABV. 3 @>:8.

5 70AB>A>2C20B8 ?VA;O 70:V=G5==O B5@ABV, 707=0G5=>3> =0 C?0:>2FV.

#<>28 715@V30==O.

15@V30B8 2 70E8I5=>ABC?=>

25 °!. 5 70<>@>6C20B8!

>?CAB8<8< T CB2>@5==O 35;5?>4V1=>W AB@C:BC@8, O:0 @C9=CTBLAO ?@8 AB@CHC20==V.

#?0:>2:0.

!;O=V D;0:>=8 B5<=>3> :>;L>@C ?> 50 <; C :0@B>==V9 C?0:>2FV.

0B53>@VO 2V4?CA:C.

0 @5F5?B>

8@>1=8:.

> «C30=AL:0 >1;0A=0 «\$0@<0FVO», D0@<0F52B8G=0 D01@8:0.

VAF57=0E>465==O 28@>1=8:0.

#: @0W=0, 91020, 289 BC?8:, 2.

**8@>1=8:.**

C1;VG=5 0:FV>=5@=5 B>20@8AB2> «V>;V:».

VAF57=0E>465==O 28@>1=8:0.

#: @0W=0, 24321, V==8FL:0 >1;., (.

0O2=8:.

"<<<:>D0@

VAF57=0E>465==O 70O2=8:0.

#: @0W=0, 04073, A?. >A:>2AL:89, 9-.