

!" #&/

4;O <548G=>3> 70AB>AC20==O ;V:0@AL:>3> 70A>1C

(AMBROBENE®)

C:;04:

4VNG0 @5G>28=0: 0<1@>:A>;C 3V4@>E;>@84;

5 <; A8@>?C ;

4>?>28=8: c>@1VBC @>7G8=, I> =5 :@8AB0;V7CTBLAO, ?@>?V;5=3;V:>;L, 0@<0B870B>@<0;8=>289, A0E0@8=, 2>40 >G8I5=0.

V:0@AL:0 D>@<0. !8@>?.

A=>2=V DV78:>-EVABV: ?@>7>@89, 15710@2=89 01> 6>2BC20B>3> :>;L>@C @>7G8= 7 <0;8=>28<0@><0B>

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, I> 70AB>A>2CNBLAO ?@8 :0H;V B0 70ABC4=8E 70E2>@N20==OE. C:>;VB8G=V 70A>18. >4 "% R05C B06.

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

\$0@<0:>48=0

<1@>:A>;C 3V4@>E;>@84 71V;LHCT A5:@5FVN 70;>7 48E0;L=8E H;OEV2. <1@>:A>; ?>A8;NT 284V;5==O ;535=52>3> AC@D0:B0=B0 H;OE× ?@O<>3> 2?;82C =0 ?=52<>F8B B8?C C 0;L25>;0E B0 ;:VB8=0E ;0@0 C 1@>=EV>;0E, 0 B0:>6 AB848BL 4> 71V;LH5==O A5:@5FVW B0 284V;5==O A;87C V ?>:@0I5==O F8;V0@=>3> ;:V@5=AC.

:B820FVO A5:@5FVW @V48=8 V 71V;LH5==OF8;V0@=>3> ;:V@5=AC ?>;53HCNBL 282545==O A;87C B0 7<5=HCNBL :0H5;L.

>2V4><;O;>AO ?@> 1;>;C20B8 =0B@VT2V :0=0;8. >A;V465==O in vitro?>:070;8, I> 0<1@>:A>;C 3V4@>E;>@84 1;>;CT =59@>==V =0B@VT2V :0=0;8; 72'O7C20==O 1C;> >1>@>B=8< V 70;56=8< 2V4 :>=F5=B@0FVW.

<1@>:A>;C 3V4@>E;>@84 ?@>45<>=AB@C202 ?@>B870?0;L=89 2?;82 in vitro >A;V465==O in vitro 28O28;8, I> 0<1@>:A>;C 3V4@>E;>@84 7=0G=> 7<5=HCT 282V;L=5==O F8B>:V=C 7 :@>2V B0 B:0=8=5 72'O7C20==O <>=>=C;:50@=8E V ?>;V<>@D=>=C;:50@=8E ;:VB8=.

>2V4><;O;>AO ?@> 7=0G=5 7<5=H5==O 1>;N V ?>G5@2>=V==O 2 3>@>;V C ?0FVT=BV2 7 D0@8=3VB> < ?@8 70AB>AC20==V ?@5?0@0BC.

VA;O 70AB>AC20==O 0<1@>:A>;C 3V4@>E;>@84C ?V428ICNBLAO :>=F5=B@0FVW 0=B81V>B8:V2 (0<>:A8F8;V=C, F5DC@>:A8=E>;535=52>

\$0@<0:>:V=5B8:0.

1A>@1FVO. 1A>@1FVO 0<1@>:A>;C 3V4@>E;>@84C 7 ?5@>@0;L=8E D>@< =5?@>;>=3>20=>W 4VW H284:0 V 4>A8BL ?>2=0, 7 ;V=V9=>N 70;56=VABN C B5@0?52B8G=>=V. 0:A8<0;L=V @V2=V C ?;072V 4>AO30NBLAO G5@57 1-2,5 3>48=8 ?@8 ?5@>@0;L=>@< H284:>3> 282V;L=5==O V 2 A5@54=L>48=8 ?@8 70AB>AC20==V D>@< ?>2V;L=>3> 282V;L=5==O.

>7?>4V;: @8 ?5@>@0;L=>7?>4V; 0<1@>:A>;C 3V4@>E;>@84C 7 :@>2V 4> B:0=8= H284:89 V @V7:> 28@065=89, 7 =0928I>N :>=F5=B@0FVTN 0:B82=>W @5G>28=8 C ;535=OE. 1'T< @>7?>4V;C ?@8 ?5@>@0;L=>28BL 552 ;. # ?;072V C B5@0?52B8G=>=V ?@81;87=> 90 % ?@5?0@0BC 72'O7CTBLAO 7 1V;:0<8.

5B01>;V7< B0 282545==O. @81;87=> 30 % 4>78 ?VA;O ?5@>@0;L=>3> 70AB>AC20==O 282>48BLAO G5@57 ?@5A8AB5<=89 <5B01>;V7

;87L:> 6 % 4>78 282>4OBLAO C =57@B>4V O: ?@81;87=> 26 % 4>78 C :>='N3>20=V9 D>@ 5@V>4 =0?V2282545==O 7 ?;07<8 :@>2V AB0=>28BL 1;87L:> 10 3>48=. 030;L=89 ;:V@5=A 7=0E>48BLAO C <560E 660 <;/E2 @07<> V7 =8@:>28< ;:V@5=A<; I> AB0=>28BL ?@81;87=> 83 % 2V4 7030;L=>3> ;:V@5=AC.

\$0@<0:>:V=5B8:0 2 >A>1;828E 3@C? E2>@8E. # ?0FVT=BV2 V7 ?>@CH5==O< DC=:FVW ?5GV=:8 282545==O 0<1@>:A>;C 3V4@>E;>@84C 7<5=H5=5, I> 7C<>2;NT 2 1,3-2 @078 28I89 @V25=L C ?;072V. A;V;L:8 B5@0?52B8G=89 4V0?07>= 0<1@>:A>;C 3V4@>E;>@84C 4>AB0B=L> H8@>:89, 77C20==O =5 ?>B@V1=>.

V: B0 AB0BL =5<0NBL ;:V=VG=> 7=0GCI>3> 2?:82C =0 D0@<0>:V=5B8:C 0<1@>:A>;C
3V4@>E;>@84C, B>@5:FVO 4>78 =5 ?>B@V1=0.
@89>< W6V =5 2?:820T =0 1V>4>ABC?=VABL 0<1@>:A>;C 3V4@>E;>@84C.

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

>:070==O.

15:@5B>;VB8G=0 B5@0?VO ?@8 3>AB@8E V E@>=VG=8E 1@>=E>?C;L<=0;L=8E 70E2>@N20==OE,
?>2'O70=8E V7 ?>@CH5==O<8 1@>=EV0;L=>W A5:@5FVW B0 >A;01;5==O< ?@>AC20==O A;87C.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> 0<1@>:A>;C B0/01> V=H8E :=5=BV2 ?@5?0@0BC.

V4:VA=V A?04:>2V AB0=8, G5@57 O:V<>6;820 =5AC?>N @5G>28=>N ?@5?0@0BC (482. @>74V;
«A>1;82>ABV 70AB>AC20==O»).

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

<1@>15=5 A8@>? =5 @5:><5=4CTBLAO ?@89<0B8 >4=>G0A=> V7 70A>10<8, I> <0NBL
?@>B8:0H;L>2C 0:B82=VABL (=0?@8:;04, :>45W=>), 1> F5 ?@872545 4> CB@C4=5==O 282545==O
<@>B8==O 7 1@>=EV2 =0 B;V 7<5=H5==O :0H;N.

0AB>AC20==O <1@>15=5 A8@>?C C ?>T4=0==V 7 0=B81V>B8:0<8 (7 0<@:A8F8;V=><, F5DC@>:A8<>
<, 5@8B@><, 4>:A8F8:;V=><) <65 ?>;V?H8B8 =04E>465==O 0=B81V>B8:V2 4> ;535=528E B:0=8=. "0:0
270T<>4VO V7 4>:A8F8:;V=>< H8@>:> 70AB>A>2CTBLAO 7 B5@0?52B8G=>N <5B>N.

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

>2V4><;O;>AO ?@> =57=0G=C :V;L:VABL 28?04:V2 @>728B:C BO6:8E H:V@=8E @50:FV9 (A8=4@>
!BV25=A0-6>=A>=0 B0 B>:A8G=89 5?V45@<0;L=89 =5:@>;V7 (A8=4@>< 09T;:0)), ?>2'O70=8E V7
70AB>AC20==O< 2V4E0@:C20;L=8E 70A>1V2, B0:8E O: 0<1@>:A>;C 3V4@>E;>@84. 451V;LH>3> WE
<>6=0 1C;> ?>OA=8B8 BO6:VABN ?5@51V3C >A=>2=>3> 70E2>@N20==O C ?0FVT=BV2 V/01>
>4=>G0A=8< 70AB>AC20==O< V=H>3> ?@5?0@0BC. ">02V =>28E C@065=L H:V@8 01> A;87>28E
>1>;>=: A;V4 =5309=> 725@=CB8AO 70 <548G=>N 4>?><3>N B0 ?@8?8=8B8 ;V:C20==O 0<1@>:A>;C
3V4@>E;>@84>

0 ?>G0B:>2V9 AB04VW A8=4@>=A>=0 01> A8=4@>

A:V;L:8 0<1@>:A>; <65 ?>A8;N20B8 A5:@5FVN A;87C, <1@>15=5 A8@>? A;V4 70AB>A>2C20B8 7
>15@56=VABN ?@8 ?>@CH5==V 1@>=EV0;L=>W<>B>@8:8 B0 ?>A8;5=V9 A5:@5FVW A;87C
(=0?@8:;04, ?@8 B0:>@N20==V O: ?5@28==0 F8;V0@=0 48A:V=57VO).

E2>@8E V7 BO6:>N =8@:>2>N =54>AB0B=VABN <>6;825 =0:>?8G5==O ?5GV=:>28E <5B01>;VBV2 0
<1@>:A>;C. 0FVT=B0< V7 ?>@CH5==O<8 DC=:FV9 =8@>: B0 BO6:8<8 70E2>@N20==O<8 ?5GV=:8
A;V4 70AB>A>2C20B8 0<1@>:A>; BV;L:8 ?VA;O :=AC;LB0FVW 7 ;V:0@# FL<>5=4CTBLAO 7
<5=HC20B8 4>7C B0 71V;LHC20B8 G0A <0<8 ?@5?0@0BC.

>B@V1=0>15@56=VABL 4;O ?0FVT=BV2 V7 28@07:0<8 H;C=:0 01> 420=04FOB8?0;>W :8H:8.

?0FVT=BV2 7 0AB<>N B0 A5@9>7=8<8 0AB<0B8G=8<8 =0?040<8 0<1@>:A>; C 283;04V A8@>?C
A;V4 70AB>A>2C20B8 7 >15@56=VABN.

<1@>15=5 A8@>? @1VB. 5 <; A8@>?C 2,1 3 A>@1VBC (I> 2V4?>2V40T 0,18 %) V T 465@5;>< 0,53 3
D@C:B>78. 0FVT=B0< V7 @V4:VA=8<8 A?04:>28<8 D>@<0<8 =5?5@5=>A8<>ABV D@C:B>78 =5 A;V4
?@89<0B8 F59 ?@5?0@0B.

<1@>15=5 A8@>? A0E0@8= =0B@VN, I> A;V4 2@0E>2C20B8 E2>@8< =0 FC:@>289 4V015B.

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

03VB=VABL

<1@>:A>;C 3V4@>E;>@84 ?@>=8:0T G5@57 ?;0F5=B0@=89 10@T@.

0=8E I>4> 70AB>AC20==O 0<1@>:A>;C 203VB=8< 6V=:0< 4>B5?5@ =54>AB0B=L>, >A>1;82> 4;O
?5@V>4C 4> 28 B86=O 203VB=>ABV. <1@>:A>; =5 ?@>45<>=AB@C202 =VO:8E B5@0B>35==8E
5D5:BV2 C E>4V 4>A;V465=L =0 B20@8=0E.

4=0: A;V4 4>B@8 728G=8E 70AB5@56=8E 70E>4V2 ?@89>4 203VB=>ABV. A>1;82> 2I B@8<5AB@V
203VB=>ABV =5 @5:><5=4CTBLAO 70AB>A>2C20B8 F59 ?@5?0@0B.

>4C20==O 3@C44N

<1@>:A>;C 3V4@>E;>@84 ?@>=8:0T C 3@C4=5 <>;>: . %>G0 =5 >GV:CTBLAO =51060=>3> 2?;82C =0 =5<>2;OB, 0<1@>:A>; =5 @5:><5=4CTBLAO 70AB>A>2C20B8 C ?5@V>4 3>4C20==O 3@C44N.

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

5<0T 40=8E I>4> 2?;82C =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. >A;V465==O 2?;82C =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8 =5 ?@>2>48;8AO.

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

<1@>15=5 A8@>? ?@89<0B8 2=CB@VH=L> ?VA;O W48. VA;O ?@89<5=4CTBLAO 28?8B8 1 A.;O=:C 2>48. C:>;VB8G=89 5D5:B 0<1@>:A>;C ?>A8;NTBLAO ?@8 26820==V 25;8:>W :V;L:>ABV @V48=8. >@>A;V B0 4VB8 2V:>< 2V4 12 @>:V2: C ?5@HV 2-3 4>18 ?> 10 <; 3 @078 =0 4>1C, 40;V ?> 10 <; 2 @078 =0 4>1C. # @07V =5>1EV4=>ABV B5@0?52B8G=89 5D5:B 4;O 4>@>A;8E B0 4VB59 2V:> 2V4 12 @>:V2 <>65 1CB8 ?V4A8;5=89 71V;LH5==O< 4>78 4> 20 <; 2 @078 =0 4>1C. >@>A;8< B0 4VBO< 2V:> 2V4 12 @>:V2 4>FV;L=> 70AB>A>2C20B8 ;V:0@AL:C D>@ =F5=B@0FVN 0 <1@>:A>;C 3V4@>E;>@84C (=0?@8::04, <1@>15=5 @>7G8= 37,5 <3/5 <);.

VB8:

2V4 2 4> 6 @>:V2 ?> 2,5 <; 3 @078 =0 4>1C; 2V4 6 4> 12 @>:V2 ?> 5 <; 2-3 @078 =0 4>1C.

"@820;VABL ;V:C20==O 70;568BL 2V4 >A>1;82>AB59 ?5@51V3C 70E2>@N20==O.

<1@>15=5 A8@>? =5 A;V4 70AB>A>2C20B8 4>2H5 4-5 4=V2 157 :>=AC;LB0FVW 7 ;V:0@5

VB8.

0AB>A>2CNBL 4VBO< 2V:> 2V4 2 @>:V2.

5@54>7C20==O.

0 40=89 G0A =5<0T ?>2V4><;5=L I>4> A?5F8DVG=8E A87C20==O C ;N459. !8<8, 2V4>>48=>:8E ?>2V4><;5=L ?@> ?5@54>7C20==O V/01> 28?04:8 ?><8;>2>3> 70AB>AC20==O ;V:V2, 2V4?>2V40NBL 2V4><8< ?>1VG=8< 5D5:B0< 0<1@>:A>;C C @5:><5=4>20=8E 4>70E V ?>B@51CNBL A8<0B8G=>3> ;V:C20==O. 091V;LH G0AB8<8 1C;8 :>@>B:>G0A=89 =5A?>:V9 B0 4V0@50.

3V4=> 7 4>;V=VG=8<8 4>A;V465==O<8, ?@8 7=0G=>7C20==V <>6CBL 28=8:0B8 ?V428I5=5 A;8=>284V;5==O, =C4>B0, 1;N20==O B0 0@B5@V0;L=0 3V?>B5=7VO.

>1VG=V @50:FVW.

I>:C VW A8AB5<8: @50:FVW 3V?5@GCB;82>ABV, C B.G.28A8?, @50:FVW 7 1>:C A;87>28E >1>;>=>;, 0=3V>=52@>B8G=89 =01@O:, 48A?=>5, A25@1V6, 0;5@3VG=V @50:FVW.=0DV;0:B8G=V @50:FVW, 2;;NG0NG8 0=0DV;0:B8G=89 H>;. :@>?82'O=:C.

I>:C =5@2>2>W A8AB5<8: 48A3527VO.

I>:C 48E0;L=>W A8AB5<8: @8=>@50, ACEVABL 48E0;L=8E H;OEV2,3V?5AB57VO 3;>B:8.

I>:C B@02=>W A8AB5<8: H;C=:>2>-:8H:>2V @>7;048 (=0?@8::04, =C4>B0, 1;N20==O, 48A?5?AVO, ?5GVO, 1V;L B0 48A:>@B C 682>BV, 70?>@, 4V0@50), ACEVABL C @>BV?>@CH5==O A<0:C, 3V?5@A0;V20FVO, 3V?5AB57VO @>B>2>W ?>@>6=8=8.

I>:C H:V@8 B0 ?V4H:V@=>W :;VB:>28=8: 5@8B5<0, 28A8?, :>=B0:B=89 45@<0B8B. >2V4><;O;>AO ?@> BO6:V C@065==O H:V@8: A8=4@> !BV25=A0-6>=A>=0 B0 A8=4@> 09T;;0, ?>2'O70=V V7 70AB>AC20==O< ;VB8G=8E 70A>1V2, B0:8E O: 0<1@>:A>;. 451V;LH>3> WE <>6=0 1C;> ?>OA=8B8 BO6:VABN ?5@51V3C >A=>2=>3> 70E2>@N20==O 01> >4=>G0A=8< 70AB>AC20==O< V=H>3> ?@5?0@0BC.

I>:C =8@>: B0 A5G>284V;L=>W A8AB5<8: 487C@VO.

030;L=V @>7;048: 3>;>2=89 1V;L, =5?@8B<=VABL, 30@OG:0, >7=>1.

"5@ABV.5 @>:V2.

VA;O ?5@H>3> 2V4:@8BBO D;0:>=0 1 @V:.

#<>28 715@V30==O.

V:0@AL:89 70AV1 =5 ?>B@51CT A?5FV0;L=8E G<>2 715@V30==O. 15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 100 <; A8@>?C C D;0:>=V; ?> 1 D;0:>=C @07< V7

0B53>@VO 2V4?CA:C. 57 @5F5?B0.

8@>1=8:.

5@:;5 <1%.

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

N42V3-5@:;5-(B@0AA5 3, 89143 ;0C1>9@5=, V<5GG8=0.