

!" #&/  
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC  
!"®  
(RISPOLEPT®)

!::04:

4VNG0 @5G>28=0: risperidone;  
1 B01;5B:0, 2:@8B0 >1>;>=:>N,  
4>?>28=8: ;0:B>70, <>=>3V4@0B; :@>E<0;L :C:C@C470=89; F5;N;>70 :@8AB0;VG=0; 3V?@><5;>70;  
<03=VN AB50@0B; :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89; =0B@VN ;0C@8;AC;LD0B; B8B0=C  
4V>:A84 (171); B0;L;; ?@>?V;5=3;V:>;L; >@0=652>-6>2B89S (110).

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV >1>;>=:>N.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B8?A8E>B8G=V 70A>18. >4 "% N05%08.

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

>:070==O.

- ;V:C20==O H87>D@5=VW B0 V=H8E ?A8EVG=8E @>7;04V2, C B>AB5@V30;0AO 2V4?>2V4L =0  
B5@0?VN, 7 <5B>N 70?>1V30==O @5F8482C E2>@>18;  
- ;V:C20==O <0=V0:0;L=8E 5?V7>4V2 ?@8 1V?>;O@=8E @>7;040E (4>?<1V=0FVW 7 =>@<>B8  
- :>@>B:>G0A=5 ;V:C20==O 28@065=>W 03@5AVW 01> BO6:8E ?A8EVG=8E A8@8 VA=C20==V  
703@>78 70?>4VO==O H:>48 A>1V G8 V=H8<;  
- A8<0B8G=5 ;V:C20==O 7CE20;8E >?>78FV9=8E @>7;04V2 01> V=H8E @>7;04V2 A>FV0;L=>W  
?>254V=:8 C 4VB59, ?V4;VB:V2 B0 4>@>A;8E 7 @>7C<>28< @>728B:<< =86G5 A5@54=L>3> 01> @>7C  
<>2>N 2V4AB0;VABN, O:V <0NBL ?@>O28 45AB@C:B82=>W ?>254V=:8 (V03@5AVO);  
- A8<0B8G=5 ;V:C20==O 0CB8G=8E @>7;04V2 C 4VB59 2V:< 2V4 5 @>:V2, C O:8E A8<8 20@VNNBL  
2V4 3V?5@0:B82=>ABV 4> @>74@0B>20=>ABV (2:;NG0NG8 03@5AVN, 70240==O A>1V BV;5A=8E  
CH:>465=L, B@82>6=VABL B0 ?0B>;>3VG=V F8;;VG=V 4VW).

@>B8?>:070==O.

V?5@GCB;82VABL 4> 0:B82=>3> :>5=BC 01> 4> 1C4L-O:>W 4>?>W @5G>28=8 C A:;04V ?@5?0@0BC.

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

28G09=0 4>70

8A?>;5?B® <>6=0 70AB>A>2C20B8 >48= 01> 420 @078 =0 4>1C. >78 1V;LH5 =V6 8 <3 A;V4 @>74V;OB8  
=0 420 ?@89><8 (2@0=FV B0 225G5@V).

;O 4>AO3=5==O 4>78 0,25 2,5 <3 @5:><5=4CTBLAO 70AB>A>2C20B8 8A?>;5?B®, @>7G8= >@0;L=89.

(87>D@5=VO

>@>A;V (2V:>< 4> 65 @>:V2)

8A?>;5?B® <>6=0 ?@87=0G0B8 >48= 01> 420 @078 =0 4>1C.

>7?>G8=0B8 ?@89>< A;V4 7 2 <3 8A?>;5?B® =0 4>1C, =0 4@C389 45=L 4>7C <>6=0 71V;LH8B8 4> 4  
<3. VA;O FL>3> 4>7C <>6=0 ?V4B@8, 70 =5>1EV4=>ABV, ?@>4>26C20B8 V=482V4C0;L=C :>@5:FVN  
4>78. ;O 1V;LH>ABV ?0FVT=BV2 @5:><5=4>20=0 4>70 AB0=>28BL 4-6 <3 =0 4>1C. 5O:8< ?0FVT=B0<  
<>65 1CB8 ?>:070=5 ?>ABC?>25 ?V428I5==O 4>78 01> 7=865=0 ?>G0B:>20 4>70.

0:A8<0;L=0 4>1>20 4>70 ?@5?0@0BC AB0=>28BL 10 <3.

>78, O:V ?5@528ICNBL 10 <3 =0 4>1C, =5 28O28;8 28I>W 5D5:B82=>ABV ?>@V2=O=> 7 <5=H8<8 4>70  
<8, 0;5 2>=8 <>6CBL A?@8G8=OB8 ?>O2C 5:AB@0?V@07, I> ?5@528ICNBL 16 <3 =0 4>1C, =5  
282G0;0AL, 4>78, I> ?5@528ICNBL F59 @V25=L, 70AB>A>2C20B8 =5 <>6=0.

0FVT=B8 ;VB=L>3> 2V:C (2V:>< 2V4 65 @>:V2).

5:><5=4>20=0 ?>G0B:>20 4>70 ?> 0,5 <3 420 @078 =0 4>1C. # @07V =5>1EV4=>ABV 4>7C <>6=0

71V;LH8B8 4> 1-2 <3 420 @078 =0 4>1C H;OE>< ?V428I5==O =0 0,5 <3 420 @078 =0 4>1C. # @07V

=5>1EV4=>ABV 4>40B:>2>W A540FVW <>6=0 >4=>G0A=> 70AB>A>2C20B8 15=7>4V075?V=.

0=V0:0;L=V 5?V7>48 ?@8 1V?>;O@=8E @>7;040E (4>@>A;V B0 4VB8 2V:< 2V4 10 @>:V2).

5:><5=4>20=0 ?>G0B:>20 4>70 8A?>;5?B® 2 <3 >48= @07 =0 4>1C, 225G5@V. >7C <>6=0

V=482V4C0;L=> 71V;LH8B8 4>4020==O< 1 <3/4>1C =5 G0ABVH5 =V6 G5@57 :>6=V 24 3>48=8. 5:>

<5=4>20=89 4V0?07>= 4>7 2V4 2 4> 6 <3 =0 4>1C.

/: V ?@8 V=H8E 2840E A8<0B8G=>3> ;V:C20==O, ?@8 4>23>B@820;>AC20==V 8A?>;5?B®

=5>1EV4=> ?5@V>48G=> ?5@53;O40B8 4>78 V :>@83C20B8 WE ?@>BO3<< CAVTW B5@0?VW. 5<0T  
 40=8E I>4> 5D5:B82=>ABV 8A?>;5?BC® ?@8 ;V:C20==V 3>AB@>W 1V?>;O@=>W<0=VW  
 B@820;VABN ?>=04 12 B86=V2. /:I> 8A?>;5?B® 70AB>A>2CNBL C :<1V=0FVW 7 =>@<>B8 C ?5@HV  
 B86=V B5@0?VW. 02VBL ?VA;O ?>O28 ?5@H>W 2V4?>2V4V =0 ;V:C20==O A;V4 2@0E>2C20B8  
 <>6;82VABL ?>2B>@=>3> 28=8:=5==O A8 45?@5AVW G5@57 >A>1;82>ABV ?5@51V3C E2>@>18 B0  
 ?>1VG=V @50:FVW ;V:0@AL:8E 70A>1V2, I> 70AB>A>2C20;8AL 4;O ;V:C20==O, C B>;5?BC®.  
 >@>B:>G0A=0 B5@0?VO 28@065=>W 03@5AVW 01> BO6:8E ?A8EVG=8E A8  
 5:<5=4>20=0 ?>G0B:>20 4>70 0,25 <3 420 @078 =0 4>1C. 0 =5>1EV4=>ABV 4>7C <>6=0 71V;LH8B8  
 H;OE<< ?V428I5==O 4>78 =0 0,25 <3 420 @078 =0 4>1C =5 G0ABVH5 =V6 G5@57 45=L. ;O 1V;LH>ABV  
 ?0FVT=BV2 >?B8<0;L=>N 4>7>N T 0,5 <3 420 @078 =0 4>1C. 4=0: 4;O 45O:8E ?0FVT=BV2 5D5:B82=C  
 4>7C <>6=0 71V;LH8B8 4> 1 <3 42VGV =0 4>1C. VA;O 4>AO3=5==O >?B8<0;L=>W 4>78 <>6=0  
 @>73;O=CB8 <>6;82VABL ?@89>1>2>W 4>78 >48= @07 =0 45=L.  
 V4;5?B<<® ?>28==0 2V41CB8AO =5 ?V7=VH5 =V6 G5@57 B@8 G0B:C B5@0?VW, B5@0?VN <>6=0  
 ?>=>28B8 ;8H5 C @07V, O:I> ?>254V=:>2V @>7;048 7O2;ONBLAO 7=>2C.

/8<0B8G=5 ;V:C20==O @>7;04V2 A>FV0;L=>W ?>254V=:8 01> 03@5A82=>W ?>254V=:8  
 0FVT=B8 7 <0A>N BV;0 >50 :3

5:<5=4>20=0 ?>G0B:>20 4>70 AB0=>28BL 0,5 <3 >48= @07 =0 45=L. 0 =5>1EV4=>ABV 4>7C A;V4  
 :>@83C20B8 H;OE<< 4>4020==O 0,5 <3 >48= @07 =0 45=L =5 G0ABVH5 =V6 G5@57 45=L. ?B8<0;L=0  
 4>70 4;O 1V;LH>ABV ?0FVT=BV2 1 <3 >48= @07 =0 45=L. 4=0: 4;O 45O:8E ?0FVT=BV2 4;O  
 4>AO3=5==O ?>78B82=>3> 5D5:BC 4>AB0B=L> =5 1V;LH5 0,5 <3 >48= @07 =0 45=L, B>4V O: V=HV  
 <>6CBL ?>B@51C20B8 1,5 <3 >48= @07 =0 45=L.

0FVT=B8 (4VB8 2V:>< 2V4 5 @>:V2 B0 4>@>A;V) 7 <0A>N BV;0 < 50 :3

5:<5=4>20=0 ?>G0B:>20 4>70 0,25 <3 >48= @07 =0 45=L. 0 =5>1EV4=>ABV 4>7C <>6=0 :>@83C20B8  
 H;OE<< 4>4020==O 0,25 <3 >48= @07 =0 45=L =5 G0ABVH5 =V6 G5@57 45=L. ?B8<0;L=0 4>70 4;O  
 1V;LH>ABV ?0FVT=BV2 0,5 <3 >48= @07 =0 45=L. 4=0: 4;O 45O:8E ?0FVT=BV2 4>AB0B=L> =5 1V;LH5  
 =V6 0,25 <3 >48= @07 =0 4>1C 4;O 4>AO3=5==O ?>78B82=>3> 5D5:BC, B>4V O: V=HV <>6CBL  
 ?>B@51C20B8 0,75 <3 >48= @07 =0 45=L.

/: V ?@8 V=H8E 2840E A8<0B8G=>3> ;V:C20==O, 4>23>B@820;5 70AB>AC20==O 8A?>;5?BC®  
 =5>1EV4=> ?5@V>48G=> ?5@53;O40B8 V :>@83C20B8 ?@>BO3<< CAVTW B5@0?VW.

CB87< (4VB8 2V:>< 2V4 5 @>:V2)

>7C A;V4 ?V418@0B8 V=482V4C0;L=>, 70;56=> 2V4 AB0=C ?0FVT=B0 B0 ;;V=VG=>W 2V4?>2V4V.  
 0FVT=B8 7 <0A>N BV;0 <50 :3

5:<5=4>20=0 ?>G0B:>20 4>70 AB0=>28BL 0,25 <3 >48= @07 =0 45=L. 4 4=O 4>7C <>6=0 71V;LH8B8 =0  
 0,25 <3. !;V4 ?V4B@87C 0,5 <3 B0 =0 14 45=L ?@>25AB8 >FV=:C ;;V=VG=>W 2V4?>2V4V. 1V;LH5==O  
 4>78 =0 0,25 <3 7 V=B5@20;<< C 2 B86=V <>6=0 @>73;O40B8 ;8H5 4;O ?0FVT=BV2 7 =54>AB0B=L>N  
 ;;V=VG=>N 2V4?>2V44N.

0FVT=B8 7 <0A>N BV;0 ≥ 50 :3

5:<5=4>20=0 ?>G0B:>20 4>70 0,5 <3 >48= @07 =0 45=L. 4 4=O 4>7C <>6=0 71V;LH8B8 =0 0,5 <3.  
 !;V4 ?V4B@87C 1 <3 B0 =0 14 45=L ?@>25AB8 >FV=:C ;;V=VG=>W 2V4?>2V4V. 1V;LH5==O 4>78 =0 0,5  
 <3 7 V=B5@20;<< C 2 B86=V <>6=0 @>73;O40B8 ;8H5 4;O ?0FVT=BV2 7 =54>AB0B=L>N ;;V=VG=>N  
 2V4?>2V44N.

>78 8A?>;5?BC® 4;O 4VB59 7 0CB87<<< (4>1>20 4>70 2 <3/45=L)

0A0 BV;0	>G0B:>20 4>70 (4=V 1-3)	5:<5=4>20=0 ?V4B@870 (4=V 4-14+)	1V;LH5==O 4>78 (70 =5>1EV4=>ABV)	V0?07>= 4>7
< 50 :3	0,25 <3	0,5 <3	+0,25 <3 7 V=B5@20;<< ≥ 2 B86=V	< 20 :3: 0,5-1,25 <3 ≥ 20 :3: 0,5-2,5 <3*
≥ 50 :3	0,5 <3	1,0 <3	+0,5 <3 7 V=B5@20;<< ≥ 2 B86=V	1,0-2,5 <3*

\* 0FVT=B8 7 <0A>N BV;0 1V;LH5 45 :3 <>6CBL ?>B@51C20B8 1V;LH8E 4>7;<0:A8<0;L=0 4>70, O:0  
 70AB>A>2C20;0AO ?V4 G0A ;;V=VG=8E 4>A;V465=L, AB0=>28;0 3,5 <3/45=L.

8A?>;5?B® <>6=0 70AB>A>2C20B8 >48= 01> 420 @078 =0 4>1C.

0FVT=B0<, C O:8E 28=8:0T A>=;82VABL ?VA;O ?@89A>2C20B8 4>1>2C 4>7C 8A?>;5?BC® ?5@54 A=> A;V465=L ?@81;87=> 42V B@5B8=8 4VB59 7 0CB87<>< A:0@68;8AO =0 A;01:VABL, I> >A>1;82> 2V4 AO ?@>BO3<< ?>G0B:>2>W D078 ;V:C20==O.  
/: BV;L:8 4>AO3=CB0 045:20B=0 ;V=VG=0 2V4?>2V4L, A;V4 @>73;O=CB8 <>6;82VABL ?>ABC?>2>3> 7 <5=H5==O 4>78 704;O 4>AO3=5==O >?B8<0;L=>3> 2V4=>H5==O ;V=VG=>W 5D5:B82=>ABV B0 157?5G=>ABV.

=D>@<0FVW, >B@8<0=>W ?@>BO3<< :>=B@>;L>20=8E ;V=VG=8E 4>A;V465=L, =54>AB0B=L> 4;O 287=0G5==O @5:><5=4>20=>W B@820;>ABV ;V:C20==O 8A?>;5?B×® ?0FVT=BV2 7 0CB87<> A2V4G5=89 A?5FV0;VAB ?>28=5= ?@>2>48B8 @5B5;L=89<>=VB>@8=3 AB0=C ?0FVT=B0.  
@8 28=8:=5==V BO6:8E ?>1VG=8E @50:FV9 (=0?@8;:04 5:AB@0?V@07;04V2, ?V7=L>W 48A:V=57VW 01>=5:>=B@>;L>20=>3> 71V;LH5==O <0A8 BV;0) A;V4 7<5=H8B8 4>7C 8A?>;5?BC® 01> ?@8?8=8B8 ;V:C20==O.

;O 4>AO3=5==O 4>78 0,25-1 <3 @5:><5=4CTBLAO 70AB>A>2C20B8 8A?>;5?B®, @>7G8= >@0;L=89.  
0FVT=B8 V7 70E2>@N20==O<8 ?5GV=:8 B0 =8@>:

# ?0FVT=BV2 7 ?>@CH5==O<8 DC=:FVW =8@>: 0:B82=0 0=B8?A8E>B8G=0 D@0:FVO 282>48BLAO 7 >@30=V72V;L=VH5, =V6 C ?0FVT=BV2 V7 74>@>28<8 =8@:0<8. # ?0FVT=BV2 V7 ?>@CH5==O<8 DC=:FVW ?5GV=:8 :>=F5=B@0FVO 2V;L=>W D@0:FVW @8A?5@84>=C C ?;072V 71V;LHCTBLAO. 570;56=> 2V4 ?>:070==O, F8< ?0FVT=B0< ?@87=0G0TBLAO ?>;>28=0 ?>G0B:>2>W B0 ?V4B@8W 4>7, B8B@C20==O 4>78 ?>28=> 1CB8 ?>2V;L=VH8 8A?>;5?B® ?>B@V1=> 70AB>A>2C20B8 7 >15@56=VABN 40=V9 :0B53>@VW ?0FVT=BV2.

5@5EV4 7 B5@0?VW V=H8<8 0=B8?A8E>B8G=8<8 70A>10<8.

/:I> F5 ;V=VG=> 28?@0240=>, ?V4 G0A B5@0?VW ?@5?0@0B× 8A?>;5?B® @5:><5=4CTBLAO ?>ABC?>2> ?@8?8=8B8 ?>?5@54=N B5@0?VN V=H8<8 ?@5?0@0B0<8. @8 FL> ?0FVT=B ?5@52>48BLAO 7 B5@0?VW 0=B8?A8E>B8G=8<8 ?@5?0@0B0<8 C D>@», ;V:C20==O ?@5?0@0B× 8A?>;5?B® @5:><5=4CTBLAO @>7?>G0B8 70AB>AC20==O 70W 70?;0=>20=>W V=T:FVW. 5@V>48G=> A;V4 >FV=N20B8 =5>1EV4=VABL ?@>4>265==O ?>B>G=>W B5@0?VW 0=B8?0@:V=A>=VG=8<8 ?@5?0@0B0<8.

>1VG=V @50:FVW.

091V;LH G0AB8<8 ?>1VG=8<8 @50:FVO<8, ?@> O:V ?>2V4<<;OTBLAO (G0AB>B0 ≥ 10 %), T ?0@:V=A>=V7<, 3>;>2=89 1V;L B0 157A>==O.

>1VG=V @50:FVW, =02545=V =86G5, 2;:NG0NBL BV, ?@> O:V ?>2V4×;O;>AO ?V4 G0A ;V=VG=8E 28?@>1C20=L B0 C ?>AB<0@:5B8=3>2>4V. '0AB>B0 28=8:=5==O ?>1VG=8E @50:FV9: 4C65 G0AB> (≥1/10), G0AB> (≥1/100 4> <1/10), =5G0AB> (≥1/1000 4> <1/100), @V4:> (≥1/10000 4> <1/1000), 4C65 @V4:> (<1/10000) B0 =52V4<> (G0AB>BC =5 <>6=0 2AB0=>28B8 7 4>ABC?=8E 40=8E).

# :>6=V9 3@C?V ?>1VG=V @50:FVW ?@54AB02;5=V C ?>@O4:C 7<5=H5==O ABC?5=O BO6:>ABV. =D5:FVW B0 V=207VW

'0AB> ?=52<>=VO, 3@8?, 1@>=EVB, V=D5:FVW 25@E=VE 48E0;L=8E H;OEV2, V=D5:FVW A5G>282V4=8E H;OEV2.

5G0AB> A8=CA8B, 2V@CA=0 V=D5:FVO, V=D5:FVW, V=D5:FVO 2CE0, B>=78;VB, F5;N;VB, >B8B A5@54=L>3> 2CE0, V=D5:FVO >:0, >:0;V7>20=0 V=D5:FVO, 0:@>45@<0B8B, V=D5:FVW 48E0;L=8E H;OEV2, F8AB8B, >=VE>7.

V4:> E@>=VG=89 >B8B A5@54=L>3> 2CE0.

I>:C :@>2V B0 ;VW A8AB5<8

5G0AB> =59B@>?5=VO, 0=5<1>F8B>?5=VO.

V4:> 3@0=C;>F8B>?5=VO.

52V4><> 03@0=C;>F8B>7.

I>:C VW A8AB5<8

5G0AB> 3V?5@GCB;82VABL.

V4:> 3V?5@GCB;82VABL 4> ?@5?0@0BC.

52V4><> 0=0DV;0:B8G=0 @50:FVO.

I>:C 5=4>:@8==>W A8AB5<8

V4:> ?>@CH5==O A5:@5FVW 0=B84VC@5B8G=>3> 3>@<>=C.

I>:C <5B01>;V7

'0AB> ?V428I5==O 0?5B8BC, 7=865==O 0?5B8BC.

5G0AB> FC:@>289 4V015BA, 0=>@5:AVO, ?>;V48?AVO, ?V428I5==O @V2=O E>;5AB5@8=C, ?V428I5==O @V2=O B@83;VF5@84V2, 7<5=H5==O <0A8 BV;0.

V4:> 3V?>3;V:528E D5@<5=BV2, ?V428I5==O @V2=O 30<<03;CB0

C65 @V4:> 4V015B8G=89 :5B>0F84>7.

52V4><> 2>4=0 V=B>:A8:0FVO.

I>:C ?A8EV:8

C65 G0AB> 157A>==O.

'0AB> B@82>30, E28;N20==O, @>7;048 A=C, 45?@5AVO.

5G0AB> A?;CB0=VABL A2V4><>ABV, <0=VO, 7=865==O ;V1V4>, 0?0BVO, =5@2>2VABL.

V4:> 0=>@307

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

C65 G0AB> ?0@:V=A>=V7<b, 3>;>2=89 1V;L.

'0AB> 0:0B87VOb, 70?0<>@>G5==O, B@5<>@b, 48AB>=VOb, A>;82VABL, A540FVO, ;5B0@3VO, 48A:V=57VOb.

5G0AB> 2V4ACB=VABL @50:FVW =0 ?>4@07=8:8, 2B@0B0 A2V4><>ABV, A8=:>?5, ?>@CH5==O A2V4><>ABV, F5@51@>20A:C;O@=V @>7;048, B@0=78B>@=0 VH5@CH5==O C2038, 3V?5@A> <=VO, ?>ABC@0;L=5 70?0<>@>G5==O, @>7;048 @V2=>2038, ?V7=O 48A:V=57VO, @>7;048 <>2;5==O, ?>@CH5==O :>>@48=0FVW, 3V?>5AB57VO, @>7;048 A<0:>28E 2V4GCBV2, AC4><8, ?0@5AB57VO.

V4:> 7;>O:VA=89 =59@>;5?B8G=89 A8=4@<, 4V015B8G=0 :><0, F5@51@>20A:C;O@=V @>7;048, F5@51@0;L=0 VH57;048 @CEC, B@5<>@ 3>;>28, A?>B2>@5==O A<0:C.

I>:C >@30=0 7>@C

'0AB> =5GVB:VABL 7>@C.

5G0AB> :>=N=:B82VB, >G=0 3V?5@5G59, =01@O:0==O >G59, ACEVABL >G59, 71V;LH5==O A;L>7>284V;5==O, A2VB;>1>O7=L.

V4:> 7=865==O 3>AB@>B8 7>@C, 70:>GC20==O >G59, 3;0C:><0, >;:N7VO @5B8=0;L=>W 0@B5@VW.

I>:C >@30=0 A;CEC

5G0AB> 1V;L C 2CE0E, B8=VB, 25@B83>.

I>:C A5@F52>W 4VO;L=>ABV

'0AB> B0EV:0@4VO.

5G0AB> 0B@V>25=B@8:C;O@=0 1;>;:040, 1;>;:040 ?CG:0 VA0, DV1@8;OFVO ?5@54A5@4L, A8=CA>20 1@048:0@4VO, 2V4GCBBO A5@F518BBO.

I>:C AC48==>W A8AB5<8

'0AB> 0@B5@V0;L=0 3V?5@B5=7VO.

5G0AB> 3V?>B5=7VO, >@B>AB0B8G=0 3V?>B5=7VO, ?@8?;828.

V4:> ;535=5289 5<1>;V7<, B@><1>7 3;81>;8E 25=.

I>:C 48E0;L=>W A8AB5<8

'0AB> 48A?=>5, =>A>20 :@>2>B5G0, :0H5;L, 70;;045=VABL =>A0, D0@8=3>;0@8=350;L=89 1V;L.

5G0AB> A28ABOG5 48E0==O, 0A?V@0FV9=0 ?=52<>=VO, ;535=5289 70ABV9, @>7;048 48E0==O, E@8?8, =01@O:0==O 48E0;L=8E H;OEV2, 48AB>=VO.

V4:> A8=4@< =VG=>3> 0?=>5, 3V?5@25=B8;OFVO.

I>:C B@02=>W A8AB5<8

'0AB> 1;N20==O, 4V0@50, 70?>@, =C4>B0, 014>BV, 2V4GCBBO 48A:>@BC C H;C=:C, 7C1=89 1V;L.

5G0AB> 48AD03VO, 30AB@8B, =5B@8<0==O :0;C, D5:0;><0, 30AB@>5=B5@8B.

V4:> =5?@>EV4=VABL :8H5G=8:C, ?0=:@50B8B, =01@O:0==O 3C1, E59;VB.

I>:C 35?0B>1V;V0@=>W A8AB5<8

V4:> 6>2BO=8FO.

I>:C H:V@8 B0 ?V4H:V@=>W ;;VB:>28=8

'0AB> 28A8?8, 5@8B5<0.

5G0AB> 0=3V>=52@>B8G=89 =01@O:, ?>H:>465==O H:V@8, @>7;048 H:V@8, A25@1V6, 0:=5, 7;L>@C H:V@8, 0;>?5FVO, A51>@59=89 45@<0B8B, ACEVABL H:V@8, 3V?5@:5@0B>7, 5:75<0.

V4:> ;C?0.

I>:C :VAB:>2>-<O7>2>W A8AB5<8

'0AB> 0@B@0;3VO, 1V;L C A?8=V, 1V;L C :V=FV2:0E.

5G0AB> <O7>20 A;01:VABL, 1V2, ?>@CH5==O ?>AB028, A:CBVABL AC3;>1V2,<O7>2>-A:5;5B=89 1V;L C 3@C4=V9 ;;VBFV.

V4:> @014>;V7.

I>:C A5G>284V;L=>W A8AB5<8

'0AB> 5=C@57.

5G0AB> 70B@8

I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7

5G0AB> 0<5=>@50, AB0B520 48ADC=:FVO, ?>@CH5==O 5@5:FVW, ?>@CH5==O 50:C;OFVW, 30;0:B>@50, 3V=5:><0ABVO, ?>@CH5==O <5=AB@C0;L=>3> F8;;C, 203V=0;L=V 284V;5==O.

52V4><> ?@V0?V7

03VB=VABL, ?VA;O?>;>3>289 ?5@V>4 B0 =5>=0B0;L=V AB0=8

C65 @V4:> A8=4@>< 2V42>=0@>465=8E.

030;L=V @>7;048

'0AB> ?V@5:AVO, 2B<0, ?5@8D5@8G=89 =01@O.; 0AB5=VO, 1V;L C 3@C4=V9 ;;VBFV.

5G0AB> =01@O: >1;8GGO, ?>@CH5==O E>48, =5728G=V 2V4GCBBO, ?>2V;L=VABL, 3@8?>?>4V1=89  
AB0=, A?@030, 48A:>@B C 3@C4=V9 ;;VBFV, >7=>1, ?04V==O.

V4:> 35=5@0;V7>20=89 =01@O.; 3V?>B5@< 2V4;>4C C :V=V2:0E, 1V;L.

01>@0B>@=V 4>A;V465==O

'0AB> 71V;LH5==O ?@>;0:B8=C 2 :@>2V0, 71V;LH5==O <0A8 BV;0.

5G0AB> ?>4>265==O V=B5@20;C QT =0 5;5:B@>:0@4V>3@03@078 :@>2V, 71V;LH5==O B@0=A0  
78=>DV;V2, 7<5=H5==O @V2=O 35<>3;>1V=C, 71V;LH5==O :@50B8=D>AD>:V=078 :@>2V.

V4:> 7=865==O B5

a □V?5@?@>;0:B8=5

b >6CBL 28=8:0B8 5:AB@0?V@00:V=57VO, @83V4=VABL ?>B8;8G=8E<07V2, <07>20 @83V4=VABL, ?0@:V=A>=VG=0 E>40  
B0 ?>@CH5==O 3;015;O@=>3> @5D;5:AC), 0:0B87VO (=5A?>:V9, 3V?5@:V=57VO B0 A8=4@>< =5A?>:V9=8E=V3), B@5<>@,  
48A:V=57VO (<07>2V ?>A<8:C20==O, E>@5>0B5B>7, 0B5B>7 B0 ;;>=CA), 48AB>=VO.

8AB>=VO 2;;NGOT <07>2V A?07<8, 3V?5@B>=CA, :@82>H8N, <8<>2V;L=V <07>2V A:>@>G5==O,<07>2V :>=B@0:BC@8,

1;5D0@>A?07<, @CE>G=8E O1:C.; ?0@0;VG O78:0, A?07<8>1;8GGO, ;0@8=3>A?07<, B>=VN, >?VAB>B>=CA, @>B>3;>B>289

A?07<, ?;5C@>B>=CA, A?07< O78:0 B0 B@871>207>2> <0NBL 5:AB@0?V@0E>465==O.

c V4 G0A ?;0F51>:>=B@>;L>20=>3> 4>A;V465==O ?>2V4<;O;>AO ?@> FC:@>289 4V015B C 0,18 % ?0FVT=V2, O:V  
70AB>A>2C20;8 @8A?5@84>=, ?>@V2=O=> 7 0,11 % C 3@C?V, 45 70AB>A>2C20;8 ?;0F51>. 030;L=0 G0AB>B0 C 2AVE  
;V=VG=8E 28?@>1C20==OE AB0=>28;0 0,43 % C ?0FVT=V2, O:V ?@89<0;8 @8A?5@84>=.

IV;LH5==O <0A8 BV;0

>@V2=O==O :V;L:>ABV ?0FVT=V2, O:V 70AB>A>2C20;8 8A?>;5?B®, B0 ?0FVT=V2, O:V  
70AB>A>2C20;8 ?;0F51> B0 <0;8 71V;LH5==O <0A8 BV;0 =0 7 % C ?;0F51>:>=B@>;L>20=8E  
4>A;V465==OE B@820;VABN 2V4 6 4> 8 B86=V2, ?>:070;8 AB0B8AB8G=> 7=0GCIC @V7=8FN C  
G0AB>BV 28?04:V2 71V;LH5==O <0A8 BV;0 C 3@C?V ?0FVT=V2, O:V ?@89<0;8 8A?>;5?B® (18 %)  
?>@V2=O=> 7 B0:>N C ?0FVT=V2, I> 70AB>A>2C20;8 ?;0F51> (9 %). # E>4V 3-B86=528E  
?;0F51>:>=B@>;L>20=8E 4>A;V465=L C 4>@>A;8E ?0FVT=V2 7 3>AB@>N <0=VTN G0AB>B0  
71V;LH5==O <0A8 BV;0 =0 ≥ 7 % 1C;0 A?V2AB02=>N 7 B0:>N C 3@C?V, I> ?@89<0;0 8A?>;5?B® (2,5 %),  
B0 C 3@C?V, I> ?@89<0;0 ?;0F51> (2,4 %), B0 1C;0 45I> 28I>N C 3@C?V 0:B82=>3> :>=B@>;N (3,5 %).  
# ?>?C;OFVW 4VB59 7 ?>@CH5==O<8 ?>254V=:8 ?@>BO3<< 4>23>B@820;8E 4>A;V465=L <0A0 BV;0  
?0FVT=V2 71V;LHC20;0AL C A5@54=L>7,3 :3 ?VA;O 125 :3 =0 @V.: >G8=0NG8 7 12 @>:V2  
71V;LH5==O <0A8 BV;0 4;0 4V2G0B 70;8H0TBLAO 2V4 3 4> 5 :3 =0 @V.: B>4V O: E;>?FV =018@0NBL  
C A5@54=L>5 :3 =0 @V.:>

>40B:>20 V=D>@<0FVO I>4> >A>1;828E :0B53>@V9 ?0FVT=V2

>1VG=V @50:FVW C ?0FVT=V2 ;VB=L>3> 2V:C 7 45<5=FVTN 01> C 4VB59, ?@> O:V ?>2V4<;O;>AL  
7 1V;LH>N, =V6 C :0B53>@VW 4>@>A;8E ?0FVT=V2, G0AB>B>N, >?8A0=V =86G5.

0FVT=B8 ;VB=L>3> 2V:C 7 45<5=FVTN

"@0=78B>@=0 VH520A:C;O@=V @>7;048 ?>1VG=V @50:FVW, ?@> O:V ?>2V4<;O;>AO ?@>BO3<<  
;V=VG=8E 4>A;V465=L 7 G0AB>B>N 1,4 % B0 1,5 % 2V4?>2V4=> C ?0FVT=V2 ;VB=L>3> 2V:C 7 45  
<5=FVTN. :@V< FL>3>, ?@> B0:V ?>1VG=V @50:FVW ?>2V4<;O;>AO 7 G0AB>B>N ≥ 5 % C  
?0FVT=V2 ;VB=L>3> 2V:C 7 45<5=FVTN B0 7 I>=09<5=H5 7 C42VGV 28I>N G0AB>B>N, =V6 C  
V=H8E :0B53>@V9 4>@>A;8E ?0FVT=V2: V=D5:FVW A5G>282V4=8E H;OEV2, ?5@8D5@8G=89  
=01@O.; ;5B0@3VO B0 :0H5;L.

VB8

030;>< >GV:C20=V ?>1VG=V @50:FVW C 4VB59 AE>6V 7 B0:8<8 C 4>@>A;8E I>4> G0AB>B8  
28=8:=5==O, B8?C B0 ABC?5=O BO6:>ABV.

>1VG=V @50:FVW, I> A?>AB5@V30;8AO C 4VB59 (2V:< 2V4 5 4> 17 @>:V2) 7 G0AB>B>N ≥ 5 % B0  
7V I>=09<5=H5 C42VGV 28I>N G0AB>B>N, =V6 C 4>@>A;8E ?0FVT=V2: A>=;82VABL/A540FVO,  
2B><0, 3>;>2=89 1V;L, ?V428I5==O 0?5B8BC, 1;N20==O, V=D5:FVW 25@E=VE 48E0;L=8E H;OEV2,  
70::045=VABL =>A0, 014>

?>28=

VAB8BL >@0=652>-6>2B89S (E 110). >65 28::8:0B8 0;5@3VG=V @50:FVW.

5@54>7C20==O.

!8<8.

7=0:8 B0 A8<8 ?5@54>7C20==O, I> A?>AB5@V30;8AL, F5 2V4>1VG=V @50:FVW ?@5?0@0BC, I-> ?@>O2;ONBLAO C ?>A8;5=V9 D>@=;82VABL V A540FVO, B0EV:0@4VO B0 0@B5@V0;L=0 3V?>B5=7VO, 0 B0:>6 5:AB@0?V@0® C :><1V=0FVW 7 ?0@>:A5B8=> # @07V 3>AB@>3> ?5@54>7C20==O A;V4 ?@>0=0;V7C20B8 <>6;82VABL ;V:0@AL:>W 270T<>4VW :V;L:>E ?@5?0@0BV2.

V:C20==O

!;V4 70157?5G8B8 B0 ?V4B@8EV4=VABL 48E0;L=8E H;OEV2 4;O 70157?5G5==O 045:20B=>W 25=B8;OFVW B0 >:A835=0FVW. !;V4 @>73;O=CB8 <>6;82VABL ?@>820==O H;C=:0 (?VA;O V=BC10FVW, O:I> ?0FVT=B =5?@8B<=>89) B0 ?@87=0G5==O 0:B82>20=>3> 2C3V;;O @07<> V7 ?@>=>A=8< 70A>1><<=5 ?V7=VH5 =V6 70 3>48=C ?VA;O ?@89>070=5 A5@F52>-AC48==5 <>=VB>@C20==O, I> 2;;NG0T 157?5@5@2=C @5TAB@0FVN 4;O 28O2;5==O <>6;828E 0@8B 8A?>;5?B® =5 <0T A?5F8DVG=>3> 0=B84>BC. "0:8< G8=><, A;V4 28:>=C20B8 2V4?>2V4=V ?V4B@848. @B5@V0;L=C 3V?>B5=7VN B0 AC48==89 :>;0?A A;V4 ;V:C20B8 B0:8<8 70E>40<8 O: 2=CB@VH=L>25==V 2;820==O B0/01> A8;V=5@3VG=V ?@5?0@0B8. !;V4 ?@>4>26C20B8 ?>ABV9=5 <548G=5 A?>AB5@565==O B0 <>=VB>@8=3 4> <><5=BC, :>;8 ?0FVT=B >4C60T.

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

%>G0 ?V4 G0A 4>A;V465=L =0 B20@8=0E =5 1C;> 28O2;5=> @>7;04V2 @5?@>4C:B82=>W A8AB5<8, A?>AB5@V302AO >?>A5@54:>20=89 2?;>82 =0 @V25=L ?@>;0:B8=C. "5@0B>35==>3> 2?;>82C 28O2;5=> =5 1C;>. >=B@>;L>20=V 4>A;V465==O 70 CG0ABN 203VB=8E 6V=>: =5 ?@>2>48;8AO. # =>2>=0@>465=8E A?>AB5@V30;8AO >1>@>B=V 5:AB@0?V@0=) 70AB>A>2C20;8AO <0BV@N ?@>B03<< >AB0==L>3> B@8<5AB@C 203VB=>ABV. &V A8<8 2;;NG0;8 068B0FVN, =5728G=> ?V428I5=89 01> 7=865=89 <07>289 B>=CA, B@5<>@, A>=;82VABL, @>7;048 48E0==O 01> ?@>1;5<8 7 3>4C20==O: G0AC, C 450:8E ?>B@51C202AO <>=VB>@8=3 AB0=C =5<>2;OB C 2V44V;5==V V=B5=A82=>W B5@0?VW 01> B@820;0 3>A?VB0;V70FVO. 8A?>;5?B® =5 @5:><5=4CTBLAO 70AB>A>2C20B8 ?V4 G0A 203VB=>ABV, >:@V< 28?04:V2 68BBT2>W =5>1EV4=>ABV. !:I> =5>1EV4=> ?@8?8=8B8 ;V:C20==O 8A?>;5?B<® ?V4 G0A 203VB=>ABV, =5 A;V4 @>18B8 F5 @0?B>2>. # E>4V 4>A;V465=L =0 B20@8=0E @8A?5@84=>= V 9-3V4@>:A8@8A?5@84=>= 284V;O;8AL C 3@C4=5 <>;>:. A?>AB5@565==O, I> @8A?5@84=>= V 9-3V4@>:A8@8A?5@84=>= <>6CBL B0:>6 284V;OB8AL C 3@C4=5 <>;>: ;N48=8 C =525;8:8E :V;L:>ABOE. # >:@5<8E 28?04:0E 4,3 % 4>78, O:C 70AB>A>2C20;0 <0B8, C 283;04V 0:B82=>W 0=B8?A8E>B8G=>W D@0:FVW 4VNG>W @5G>28=8 287=0G0;>AL C 3@C4=>4C20==O 3@C44N A;V4 ?@8?8=8B8.

VB8.

@5?0@0B 70AB>A>2CNBL 4;O A8<0B8G=>3> ;V:C20==O 28;;NG=> @>7;04V2 A>FV0;L=>W ?>254V=:8, 7CE20;>->?>78FV9=8E @>7;04V2 01> V=H8E @>7;04V2 A>FV0;L=>W ?>254V=:8, 0 B0:>6 0CB8G=8E @>7;04V2 ?>254V=:8 4VBO< 2V:<< 2V4 5 @>:V2.

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

V428I5=89 @V25=L ;5B0;L=>ABV C ?0FVT=BV2 ;VB=L>3> 2V:C 7 45<5=FVTN. !5@54 ?0FVT=BV2 ;VB=L>3> 2V:C 7 45<5=FVTN, O:V ;V:C20;8AL 0B8?>28<8 0=B8?A8E>B8G=8<8 ?@5?0@0B0<8, A?>AB5@V302AO ?V428I5=89 @V25=L ;5B0;L=>ABV ?>@V2=O=> 7 B0:8< C ?0FVT=BV2 7 3@C?8 ?;0F51> 2 <5B0=0=0;V7V 17 :>=B@>;L>20=8E 4>A;V465=L 0B8?>28E 0=B8?A8E>B8G=8E ?@5?0@0BV2, 2;;NG0NG8 8A?>;5?B®. # ?;0F51>:>=B@>;L>20=>A;V465==V V7 70AB>AC20==O< ?@5?0@0BC 8A?>;5?B® E2>@8< FVTW :0B53>@VW G0AB>B0 28?04:V2 ;5B0;L=>ABV AB0=>28;0 4,0 % ?>@V2=O=> 7 3,1 % C 3@C?V ?;0F51>. !5@54=V9 2V: ?0FVT=BV2, O:V ?><5@;8, 1C2 86 @>:V2 (4V0?07>= 67-100 @>:V2). 57C;LB0B8 42>E 25;8:8E >3;O4>28E 4>A;V465=L ?>:070;8, I> ?0FVT=B8 ;VB=L>3> 2V:C 7 45<5=FVTN, O:V ;V:C20;8AL 728G09=8<8 0=B8?A8E>B8G=8<8 70A>10<8, <0NBL <0;89 ?V428I5=89 @878: ;5B0;L=>ABV, ?>@V2=O=> 7 B8<8, O:V =5 ;V:C20;8AL. 5 VA=CT ?>2=8E 40=8E, 73V4=> 7 O:8<8 <>6=0 40B8 AC2>@C >FV=:C @V2=O @878:C, 4> B>3> 6, ?@8G8=0 ?V428I5=>3> @878:C =52V4><0. 5<>6;82> GVB:> 287=0G8B8 <0AHB01, =0 O:89 <>6=0 ?>H8@8B8 @57C;LB0B8 >3;O4>28E 4>A;V465=L, O:V AB>ACNBLAO ?V428I5=>W A<5@B=>ABV, ?>2070=>W V7 70AB>AC20==O< 0=B8?A8E>B8G=>3> ?@5?0@0BC O: ?@>B82038 ?52=8<(/V9) E0@0:B5@8AB8:0<(/V) ?0FVT=BV2.

?O@=V ?>1VG=V 5D5:B8.

878: F5@51@>20A:C;O@=8E ?>1VG=8E 5D5:BV2 7=0G=> 28I89 C ?0FVT=BV2 7V 7N 01> AC48==>N 45  
<5=FVTN 2 ?>@V2=O==V 7 45<5=FVTN ;LF359<5@0. "0:8< G8=><, C ?0FVT=BV2 7 V=H8<8 B8?0<8 45  
<5=FVW 8A?>;5?B® 70AB>A>2C20B8 =5 @5:><5=4>20=>.

8A?>;5?B® ?>B@V1=> 28:>@8AB>2C20B8 BV;L:8 ?@>BO3< :>@>B:>3> B5@N B0 206:>N 45  
<5=FVTN ;LF359<5@0 =0 4>40B>: 4> =5D0@<0:>;>3VG=>3> ;V:C20==O, O:5 1C;8 >1<565=8< 01>  
=55D5:B82=8< V, :>;8 ?@8ACB=V9 ?>B5=V9=89 @878: 70?>4VO==O H:>48 A>1V G8 V=H8  
0FVT=B8 ?>28==V @53C;O@=> >3;O40B8AO C ;V:0@O 4;O >FV=:8 =5>1EV4=>ABV ?@>4>265==O  
;V:C20==O.

# E>4V ?;0F51>:>=B@>;L>20=8E ;V=VG=8E 4>A;V465=L A5@54 ?0FVT=BV2 7 45<5=FVTN, O:8E  
;V:C20;8 8A?>;5?B® A?>AB5@V302AO 28I89 @V25=L F5@51@>20A:C;O@=8E ?>1VG=8E 5D5:BV2  
(F5@51@>-20A:C;O@=V B0 <8=CIV VH5 (A5@54=V9 2V: 85 @>:V2; 2V:>289 ?@>. 73-97 @>:V2).

><1V=>20=V 40=V H5AB8 ?;0F51>:>=B@>;L>20=8E 4>A;V465=L C ?0FVT=BV2 ;VB=L>3> 2V:C 7 45  
<5=FVTN (2V:>< 2V4 65 @>:V2) ?@>45<=>AB@C20;8 28=8:=5==O F5@51@>20A:C;O@=8E @>7;04V2  
C 3,3 % (33/989) ?0FVT=BV2, O:V ;V:C20;8AO 8A?>;5?B® ?>@V2=O=> 7 1,2 % (8/693) ?0FVT=BV2,  
O:V 70AB>A>2C20;8 ?;0F51>. !;V4 @5B5;L=> 72068B8 2AV @878:8 B0 ?5@52038 ?@87=0G5==O  
8A?>;5?B® >A>1;82> D0:B>@8 @878:C A5@F52>3> =0?04C. >A>1;82>N >15@56=VABN A;V4  
?@87=0G0B8 8A?>;5?B® ?0FVT=B0< 7 45<5=FVTN, C O:8E =0O2=0 0@B5@V0;L=0 3V?5@B5=7VO,  
70E2>@N20==O A5@F52>-AC48==>W A8AB5<8, B0 ?0FVT=B0< 7 AC48==>N 45<5=FVTN. !;V4  
?@>V=AB@C:BC20B8 ?0FVT=BV2 B0 >AV1, O:V 4>3;O40NBL 70 =8<8, =5309=> ?>2V4<>;OB8 ?@>  
>7=0:8 <>6;828E A5@F52>-AC48==8E =0?04V2, B0:8E O: @0?B>20 A;01:VABL, >=V1;8GGO, @C: 01>  
=V3, 0 B0:>6 @>7;048 <>2;5==O B0 7>@C. !;V4 =52V4;:04=> @>73;O=CB8 2AV <>6;82V 20@V0=B8  
;V:C20==O, 2;;NG0NG8 ?5@5@820==O B5@0?VW 8A?>;5?B®.

4=>G0A=5 70AB>AC20==O 7 DC@>A5

# E>4V ?;0F51>:>=B@>;L>20=>3> 4>A;V465=O C ?0FVT=BV2 ;VB=L>3> 2V:C 7 45<5=FVTN  
?V428I5=89 @V25=L ;5B0;L=>ABV A?>AB5@V302AO ?@8 >4=>G0A=>A>2C20==V DC@>A5=>< (7,3  
%; A5@54=V9 2V: 89 @>:V2, 4V0?07>= 75-97 @>:V2) ?>@V2=O=> 7 B0:8< C ?0FVT=BV2, O:V  
;V:C20;8AO BV;L:8 @8A?5@84>=>< (3,1 %; A5@54=V9 2V: 84 @>:V2, 4V0?07>= 70-96 @>:V2) 01>  
BV;L:8 DC@>A5< (4,1 %; A5@54=V9 2V: 80 @>:V2, 4V0?07>= 67-90 @>:V2). V428I5==O @V2=O  
;5B0;L=>ABV C ?0FVT=BV2, O:V ;V:C20;8AO DC@>A5< >4=>G0A=> 7 @8A?5@84>=><,  
A?>AB5@V30;>AO C E>4V 42>E ;V=VG=8E 4>A;V465=L 7 G>B8@L>E. 4=>G0A=5 70AB>AC20==O  
@8A?5@84>=C 7 V=H8<8 4VC@5B8:0<8 (2 >A=>2=>  
5 2AB0=>2;5=> ?0B>DV7V>;>3VG=8E <5E0=V70A=5==O FL>3> D0:BC. 4=0: A;V4 4>B@8A>1;82>W  
>15@56=>ABV ?@8 ?@87=0G5==V ?@5?0@0BC C B0:8E 28?04:0E, 0 B0:>6 ?>B@V1=> ?@>25AB8  
>FV=:C @878:V2 B0 :>@8ABV FVTW :><1V=0FVW 01> >4=>G0A=>3> 70AB>AC20==O 7 V=H8<8  
?>B5=V9=8<8 4VC@5B8:0<8, ?5@H =V6 ?@87=0G0B8 ?@5?0@0B. 5 28O2;5=> ?V428I5==O ?>:07=8:0  
;5B0;L=>ABV C ?0FVT=BV2, O:V >4=>G0A=> 70AB>A>2C20;8 V=HV 4VC@5B8G=V 70A>18 @07<  
V7 @8A?5@84>=> 2V4 ;V:C20==O 453V4@0B0FVO 1C;0 7030;L=8< D0:B>@< @878:C ;5B0;L=>ABV,  
V WW A;V4 @5B5;L=> :>=B@>;N20B8 C ?0FVT=BV2 7 45<5=FVTN.

VB8.

5@54 ?@87=0G5==O< 8A?>;5?B® 4VBO<, A;V4 @5B5;L=> 72068B8 A?V22V4=>H5==O @878:-  
:>@8ABL. 5>1EV4=> @53C;O@=> @5B5;L=> >FV=N20B8 ?>B@51C C ?@>4>265==V ;V:C20==O.  
>:070==O «A8<0B8G=5 ;V:C20==O @>7;04V2 A>FV0;L=>W ?>254V=:8, 7CE20;>-?>78FV9=8E  
@>7;04V2 B0 01> V=H8E @>7;04V2 A>FV0;L=>W ?>254V=:8» B0 «0CB8G=V @>7;048»  
4>A;V46C20;8AO ;8H5 C 4VB59 2V:>< 2V4 5 @>:V2. ">;5?B® 4VBO< 7 B0:8<8 ?>:070==O<8 2V:>< 4> 5  
@>:V2.

5<0T 4>A2V4C 70AB>AC20==O 8A?>;5?B® 4VBO< 2V:>< 4> 15 @>:V2 4;O ;V:C20==O H87>D@5=VW  
B0 B0 4VBO< 2V:>< 2V4 10 @>:V2 4;O ;V:C20==O <0=V0:0;L=8E 5?V7>4V2 ?@8 1V?>;O@=8E  
@>7;040E.

;O 4VB59 4>ABC?=V 40=V 107CNBLAO =0 ;V=VG=8E 4>A;V465==OE B@820;VABN 1 @V:. &V 40=V

?>:07CNBL, I>=5 2V41C20TBLAO 2?;82C=0 @VAB B0 @>728B>.: ?;82=0 @VAB B0 @>728B>: ?@8 ;V:C20==V B@820;VABN 1V;LH5 >4=>3> @>:C =52V4x89. ">2>48B8 @53C;O@=89 ;;V=VG=89 <>=VB>@8=3 5=4>:@8==>W A8AB5<8, 2;;NG0NG8 28ABC B0 <0A8 BV;0, :=B@>;L AB0B52>3> @>728B:C, ?>B5=8E ?@>;0:B8=70;56=8E 5D5:BV2, 4>A;V465==O 5:AB@0?V@028E @>7;04V2.

!>=:82VABL.

V4 G0A ?;0F51>:-:=B@>;L>20=8E 4>A;V465=L A>=:82VABL G0AB> A?>AB5@V30;0AO C 4VB59 7 0CB87<>3> 4> ?>3> ABC?5=O B06:>ABV. 5@5206=> A>=:82VABL A?>AB5@V30;0AO =0 ?>G0B:C ;V:C20==O, 7 =091V;LH>N G0AB>B>N 2?@>4>26 ?5@H8E 42>E B86=V2 ;V:C20==O, B0 A@>ABV9=> <8=0;0, A5@54=O B@820;VABL AB0=>28;0 16 4=V2. 0FVT=B0< 7 A>=:82VABL <>6=0 @>73;O=CB8 <>6;82VABL 7C20==O.

@B>AB0B8G=0 3V?>B5=7VO.

'5@57 α1-;VB8G=C 0:B82=VABL @8A?5@84>=C, >A>1;82>=0 ?>G0B:C ;V:C20==O,<>65 A?>AB5@V30B8AO >@B>AB0B8G=0 3V?>B5=7VO. # ?>AB<0@:5B8=3>2>4V ;;V=VG=> 7=0GCI0 3V?>B5=7VO A?>AB5@V30;0AL ?V4 G0A >4=>G0A=>3> 70AB>AC20==O @8A?5@84>=C B0 0=B83V?5@B5=782=8E 70A>1V2. 8A?>;5?B® A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 2V4><8<8 :0@4V>20A:C;O@=8<8 70E2>@N20==O<8 (B0:8<8 O: A5@F520 =54>AB0B=VABL, V=D0@:B :0@40, ?>@CH5==O ?@>2V4=>ABV, 453V4@0B0FVO, 3V?>2>;5F5@51@>20A:C;O@=V 70E2>@N20==O). # F8E 28?04:0E 4>7C A;V4 B8B@C20B8 (482. @>74V; <! ?>AV1 70AB>AC20==O B0 4>78»). !;V4 @>73;O=CB8 <>6;82VABL 7<5=H5==O 4>78 ?@8 28=8:=5==V 3V?>B5=7VW.

>4>265==O V=B5@20;C QT.

# ?>AB<0@:5B8=3>2>4V 4C65 @V4:> A?>AB5@V30;8AO 28?04:8 ?>4>265==O V=B5@20;C QT. !;V4 7 >15@56=VABN 70AB>A>2C20B8 8A?>;5?B®, O: V V=HV 0=B8?A8E>B8G=V 70A>18, ?0FVT=B0< V7 A5@F52>N 0@8BQT, 1@048:0@4VTN G8 ?>@CH5==O<8 5;5:B@>;VB=>3> >1:0;VT<03=VTA:V;L:8 <>65 ?V4281C20B8AO @878: 0@8B<>35==8E @50:FV9, O: V ?@8 ACQT.

V7=O 48A:V=57VO/5:AB@0?V@0

@8 70AB>AC20==V ?@5?0@0BV2 V7 2;0AB82>ABO<8 0=B03>=VABV2 4>D028E @5F5?B>@V2 2V4 AL 28=8:=5==O ?V7=L>W 48A:V=57VW, I> E0@0:B5@87CTBLAO <8<>2V;L=8<8 @8B@>< @878:C @>728B:C ?V7=L>W 48A:V=57VW. !:I> 28=8:0NBL >7=0:8 B0 A8<8 ?V7=L>W 48A:V=57VW, A;V4 @>73;O=CB8 ?8B0==O I>4> 2V4B8G=8E ?@5?0@0BV2.

%2>@>10 0@:V=A>=0 B0 45<5=FVO 7 BV;LFO<8 52V.

V:0@V ?>28==V 7206C20B8 =5157?5:C 01> :=@8ABL ?@8 ?@87=0G5==V 0=B8?A8E>B8G=8E 70A>1V2, C B>;5?BC®, ?0FVT=B0< V7 E2>@>1>N 0@:V=A>=0 01> 45<5=FVTN 7 BV;LFO<8 52V. 0AB>AC20==O @8A?5@84>=C <>65 ?>3V@H8B8 ?5@51V3 E2>@>18 0@:V=A>=0. 0FVT=B8, E2>@V =0 1C4L-O:5 V7 707=0G5=8E 28I5 70E2>@N20=L, <>6CBL <0B8 ?V42815=89 @878: =59@>;5?B8G=>3> 7;>O:VA=>3> A8=4@>6 ?V42815=C GCB;82VABL 4> 0=B8?A8E>B8G=8E ?@5?0@0BV2; B0:8E ?0FVT=8E 1C;> 28;;NG5=> 7 ;;V=VG=8E 4>A;V465=L. >40B:>2> 4> 5:AB@0?V@0

59@>;5?B8G=89 7;>O:VA=89 A8=4@>

@8 70AB>AC20==V ::0A8G=8E =59@>;5?B8G=8E ;V:0@AL:8E 70A>1V2 2V4;5?B8G=>3> 7;>O:VA=>3> A8=4@> E0@0:B5@87CTBLAO 3V?5@B5@3;>1V=C@VN (@014>;V7) B0 3>AB@5 ?>@CH5==O DC=:FVW =8@>:. # @07V @>728B:C =59@>;5?B8G=>3> A8=4@>1EV4=> 2V4B8G=V ?@5?0@0B8, 2;;NG0NG8 8A?>;5?B®.

53C;OFVO B5

=B8?A8E>B8G=V ;V:0@AL:V 70A>18 <>6CBL ?>@CHC20B8 740B=VABL BV;0 4> 7=865==O >A=>2=>W B5<5=4CTBLAO 2V4?>2V4=89 4>3;O4 ?0FVT=B0<, O:8< ?@87=0G5=> 8A?>;5?B®, O:I> 2>=8 1C4CBL ?V44020B8AO 2?;82C C<>2, I> <>6CBL A?@8G8=OB8 ?V42815==O >A=>2=>W B5:8E B5 2=VH=L>3> A5@54>28I0, AC?@>2V4=0 B5@0?VO ?@5?0@0B0<8 7 0=B8E>;V=5@3VG=>N 0:B82=VABN G8 2?;82 7=52>4=5==O.



V?5@3;V:5289 4V015B.

V?5@3;V:5 703>AB@5==O VA=CNG>3> 4V015BC 1C;8 >?8A0=V C ?>>48=>:8E 28?04:0E ?V4 G0A ;V:C20==O ?@5?0@0BV2. 8A?>;5?B®. &V ;;V=VG=V A?>AB5@565==O @5:>5=4>20=> 2@0E>2C20B8 ?0FVT=B0<, E2>@8<=0 4V015B, B0 ?0FVT=B0< 7 D0:B>@0<8 @878:C @>728B:C FC:@>2>3> 4V015BC.

59:>?5=VO, =59B@>?5=VO, 03@0=C;>F8B>7.

V4 G0A 70AB>AC20==O 0=B8?A8E>B8G=8E 70A>1V2, 2;;NG0NG8 @8A?5@84>=, A?>AB5@V30;8AL 28?04:8 ;59:>?5=VW, =59B@>?5=VW B0 03@0=C;>F8B>7C. # ?>AB<0@:5B8=3>2>4V 03@0=C;>78B>7 A?>AB5@V302AO 4C65 @V4:> (<1/10 000 ?0FVT=BV2). 0 ?0FVT=B0<8 7V 7=0GCI8< 7<5=H5==O< :V;L:>ABV 1V;8E :@>2O=8E BV;5FL 2 0=0<=57V 01> 7 <548:0<5=BV=4C:>20=>N ;59:>?5=VTN /=59B@>?5=VTN A;V4 @5B5;L=> =03;O40B8 ?@>B03< ?5@H8E 45;V;L:>E AC20==O @8A?5@84>=C O: BV;L:8 7O2;OBLAO >7=0:8 7=0GCI>3> 7<5=H5==O :V;L:>ABV 1V;8E :@>2O=8E BV;5FL B0 =5<0T V=H8E ?@8G8= 4;O 28=8:=5==O FL>3> O28I0. 0 ?0FVT=B0<8 V7 ;;V=VG=> 7=0GCI>N =59B@>?5=VTN A;V4 A?>AB5@V30B8 AB>A>2=> 28=8:=5==O 30@OG:8 B0 V=H8E >7=0: V=D5:FVW B0 ;V:C20B8 2V4?>2V4=8< G8=>< ?@8 28O2;5==V A89/; ;V:C20==O @8A?5@84>=>< A;V4 ?@8?8=8B8.

5=>7=0 B@><1>5<1>;VO.

?8A0=V 28?04:8 25=>7=>W B@><1>5<1>;VW ?@8 70AB>AC20==V 0=B8?A8E>B8G=8E ;V:0@AL:8E ?@5?0@0BV2. A;V;L:8 ?0FVT=B8, O:V ;V:CNBLAO 0=B8?A8E>B8G=8<8 ;V:0@AL:8<8 70A>10<8, G0AB> <0NBL =01CBV D0:B>@8 @878:C 28=8:=5==O 25=>7=>W B@><1>5<1>;VW, 2AV<>6;82V D0:B>@8 @>728B:C B@><1>5<1>;VW =5>1EV4=> V45=B8DV:C20B8 ?5@54 B0 ?V4 G0A ;V:C20==O 8A?>;5?B><® B0 ?@>25AB8 2V4?>2V4=V ?@525=B82=V 70E>48.

1V;LH5==O <0A8 BV;0.

# ?0FVT=BV2, I> 70AB>A>2CNBL 8A?>;5?B®, T @878: ?V428I5==O <0A8 BV;0. 5:>5=4>20=89 :>=B@>;L <0A8 BV;0.

@V0?V7<

A=CT <>6;82VABL 28=8:=5==O ?@V0?V7;5?B><® C=0A;V4>: 9>3> 0;LD0-04@5=5@3VG=>W 1;>;CNG>W 4VW.

@>B81;N2>B=89 5D5:B.

# 4>;V=VG=>AB59 @8A?5@84>=C 2V4B81;N2>B=89 5D5:B. &O 2;0AB82VABL <>65 <0A:C20B8 A8<8 ?5@54>7C20==O 45O:8E ;V:V2 01> B0:8E AB0=V2, O: >1AB@C:FVO :8H5G=8:C, A8=4@< 5O B0 ?CE;8=8 <>7:C.

>@CH5==O DC=:FVW ?5GV=:8 B0 =8@>:.

# ?0FVT=BV2 7 ?>@CH5==O< DC=:FVW =8@>: 0=B8?A8E>B8G=0 D@0:FVO 282>48BLAO ?>2V;L=VH5, =V6 C 4>@>A;8E 7 =>@<0;L=>N DC=:FVTN =8@>:.. # ?0FVT=BV2 7 ?>@CH5==O< DC=:FVW ?5GV=:8 71V;LH5=0 :>=F5=B@0FVO C ?;07W D@0:FVW @8A?5@84>=C.

V?5@?@>;0:B8=5

>A;V465==O =0 :C;LBC@0E B:0=8= 2:07CNBL =0 B5, I> @VAB ;;VB8= C ?CE;8=0E <>;>G=>W 70;>78 ;N48=8 <>65 1CB8 AB820=89 ?@>;0:B8=>G0 4>AV GVB:>3> 72O7:C AB>A>2=> 70AB>AC20==O 0=B8?A8E>B8G=8E 70A>1V2 ;;V=VG=8<8 B0 5?V45;>3VG=8<8 4>A;V465==O<8 =5 ?>:070=>, @5:> <5=4CTBLAO 7 >15@56=VABN ?@87=0G0B8 @8A?5@84>= ?0FVT=B0< 7 2V4?>2V4=>N ?0B>;>3VTN 2 0=0<=57V. 8A?>;5?B® ?>B@V1=> 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 =0O2=>N 3V?5@?@>;0:B8=5

!C4><8.

!;V4 7 >15@56=VABN 70AB>A>2C20B8 8A?>;5?B® ?0FVT=B0<, O:V <0NBL =0?048 AC4× G8 V=HV  
AB0=8 2 0=0<=57V, O:V ?>B5=V9=> 7=86CNBL AC4×=89 ?>@V3.  
>?>28=8.

"01;5B:8, 2:@8BV >1>;>=:>N, 7C. 0FVT=B8 7V A?04:>2>N =5?5@5=>A878, ;0:B07>N =54>AB0B=VABN  
01> A8=4@××× <0;L01A>@1FVW 3;N:>78-30;0:B>78 =5 ?>28==V ?@89<0B8 ?@5?0@0B 8A?>;5?B®,  
B01;5B:8, 2:@8BV >1>;>=:>N.

**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.**

8A?>;5?B® <>65 <0B8 =525;8:89 01> ?>B@0=A?>@B< C=0A;V4>: ?>B5=V9=>3> 2?;82C =0 =5@2>2C  
A8AB5@30=8 7>@C (482. @>74V; <<>1VG=V @50:FVW»). # ?>F5AV ;V:C20==O @5:×5=4CTBLAO  
CB@8B@0=A?>@B<< 01> @>1>B8 7 V=H8<8 <5E0=V7<0<8, 4>:8 =5 AB0=5 2V4×>N V=482V4C0;L=0  
GCB;82VABL ?0FVT=V2 4> ?@5?0@0BC.

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

>A;V465==O <5B01>;V7in vitro?@>45<>=AB@C20;8, I> @>7?04 @8A?5@84>=C 4> 9-3V4@>:A8-  
@8A?5@84>=C <>65 ?@83=VGC20B8AO D5=>BV078=0<8, B@8F8::VG=8<8 0=B845?@5A0=B0<8 B0  
45O:8<8 15B0-1;>:0B>@0<8, O:V 7207CNBLAO 7 CYP 2D6. "0:5 ?@83=VG5==O <>65 ?@8725AB8 4>  
71V;LH5==O :>=F5=B@0FVW @8A?5@84>=C B0 7<5=H5==O 0:B82=>3> <5B01>;VBC 9-  
3V4@>:A8@8A?5@84>=C C ?;07G0 ;V=VG=V 40=V 12 ?0FVT=V2 ?>:070;8, I> 07?04 @8A?5@84>=C  
4> 9-3V4@>:A8@8A?5@84>=C, 0=0;V7 40=8E =525;8:>W :V;L:>ABV ?0FVT=V2, O:V >4=>G0A=>  
70AB>A>2C20;8 FV ;V:0@AL:V 70A>18, ?V4B25@46CT B5, I> ;V=VG=89 5D5:B =5 7  
8A?5@84>= A;01:89 V=3V1VB>@ CYP 2D6 in vitro ">GV:CTBLAO, I> 8A?>;5?B® 1C45 ACBBT2>  
?@83=VGC20B8 282545==O ;V:0@AL:8E 70A>1V2, O:V <5B01>;V7CNBLAO F8<8 D5@<5=B0<8.  
@8 >4=>G0A=>AC20==V ;V:0@AL:8E 70A>1V2, O:V T V=4C:B>@0<8 D5@<5=V2, <5B01>;V7<  
@8A?5@84>=C <>65 71V;LHC20B8AO. 0@10<075?V= 7=86CT :>=F5=B@0FVN 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW C ?;072V. ;V=VG=V 40=V ?@>45<>=AB@C20;8, I> C ?0FVT=V2, O:V  
>4=>G0A=> 70AB>A>2C20;8 :0@10<075?V=, ?;07<>2V :>=F5=B@0FVW @8A?5@84>=C B0 9-  
3V4@>:A8-@8A?5@84>=C 1C;8 C 1,7-3,7 @070 =86GV. # ?>>48=>:8E 28?04:0E ?@8 >4=>G0A=>  
AC20==V :0@10<075?V=C B0 @8A?5@84>=C A?>AB5@V30;8AO B>:A8G=V A8@>20B:>2V  
:>=F5=B@0FVW :0@10<075?V=C. =0;>3VG=V 5D5:B8 (7=865==O :>=F5=B@0FVW 2 ?;07W  
0=B8?A8E>B8G=>W D@0:FVW) <>6CBL A?>AB5@V30B8AL ?@8 28:>@8AB0==V V=H8E  
V=4C:B>@V2 ?5GV=:>28E D5@<5=V2, B0:8E O: @8D0W= B0 D5=>10@1VB0;; O:V V=4C:CNBL  
?5GV=:>2V D5@<5=B8 CYP 34 B0: O: V -3;V:>?@>B5V=  
C;> 28O2;5=>, I> D;C>:A5B8= (20 <3/4>1C) B0 ?0@>:A5B8= (20 <3/4>1C) 71V;LHCNBL :>=F5=B@0FVN  
@8A?5@84>=C C ?;072V4=>. \$;C>:A5B8= =5 2?;820T =0 :>=F5=B@0FVN 9-3V4@>:A8@8A?5@84>=C C  
?;07:A5B8= C A5@54=L=>=F5=B@0FVN 9-3V4@>:A8@8A?5@84>=C C ?;07< :>=F5=B@0FVO 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW 71V;LHCTBLAO =0 50% ?@8 >4=>G0A=>AC20==O D;C>:A5B8=C B0  
?0@>:A5B8=C. /I> ?V4 G0A B5@0?VW 8A?>;5?B® ?@87=0G0TBLAO 01> ?@8?8=OTBLAO  
;V:C20==O D;C>:A5B8=× B0 ?0@>:A5B8=×, ;V:0@N A;V4 ?5@53;O=CB8 4>7C 8A?>;5?BC®.  
8A?5@84>= A;V4 7 >15@56=VABN 70AB>A>2C20B8 C :×1V=0FVW 7 V=H8<8 AC1AB0=FVO<8  
F5=B@0;L=>W 4VW 28;;NG=>, C B>3>;5<, >?V0B0<8, 0=B83VAB0  
8A?>;5?B® <>65 28O2;OB8 0=B03>=VAB8G=V 5D5:B8 4> ;52>4>?8 B0 V=H8E 0=B03>=VABV2 4>?0  
B0:0 :×1V=0FVO 22060TBLAO =5>1EV4=>N, >A>1;82> C B5@  
E2>@>18 0@:V=A>=0, <0NBL ?@>?8AC20B8AL =09<5=HV 5D5:B82=V 4>78.  
&8<5B848= C 4>7V 400 <3 42VGV =0 4>1C B0 @0=VB848= 150 <3 42VGV =0 4>1C 71V;LHC20;8 AUC  
0:B82=>W 0=B8?A8E>B8G=>W D@0:FVW (@8A?5@84>=C B0 9-3V4@>:A8@8A?5@84>=C) =0 8 % B0  
20 % 2V4?>2V4=>, E>G0 F5 ;V=VG=> =57=0GCI5.  
?;82 2V4:A5B8=× B0 ?0@>:A5B8=× =0 D0@<0>:V=5B8:C @8A?5@84>=C 01> 9-  
3V4@>:A8@8A?5@84>=C =5 4>A;V46C202AO.  
@8B@>@ CYP 3A4) =5 2?;820T =0 D0@<0>:V=5B8:C @8A?5@84>=C B0 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW.  
# ?>AB<0@:5B8=3>2>4V A?>AB5@V30;8AO 28?04:8 ;V=VG=> 7=0GCI>W 3V?>B5=7VW ?@8  
>4=>G0A=>AC20==V @8A?5@84>=C B0 0=B83V?5@B5=782=8E ;V:0@AL:8E 70A>1V2.

/: V 7 V=H8<8 0=B8?A8E>B8:0<8, A;V4 4>B@815@56=>ABV ?@8 ?@87=0G5==V @8A?5@84>=C 7  
;V:0@AL:8<8 70A>10<8, O:V ?>4>26CNBL V=B5@20; QT, =0?@8:;04 7 0=B80@8B<), 0=B80@8B40@>=>  
<, A>;0B>;<), B@8F8:;VG=8<8 0=B845?@5A0=B0<8 (0<), B5B@0F8:;VG=8<8 0=B845?@5A0=B0<8 (  
<0?@>;VB8=><), 450:8<8 0=B83VAB0<03=57VT10<8, O:V ?@83=VGCNBL ?5GV=:>289 <5B01>;V7<  
@8A?5@84>=C. 0=89 ?5@5;V: =5 T ?>2=8  
=3V1VB>@8 E>;V=5AB5@078, 30;0=B0=575?V; =5 28O2;ONBL ;;V=VG=> 7=0GCI8E 5D5:BV2 =0 D0@  
<0:;>V=5B8:C @8A?5@84>=C B0 0:B82=>W 0=B8?A8E>B8G=>W D@0:FVW.  
0AB>AC20==O ?A8E>AB8@V2 (=0?@8:;04, <5B8;D5=V40BC) C :><1V=0FVW 7 8A?>;5?B><® 4VBO<  
B0 ?V4;VB:0< =5 7®.  
5@0?0@ !Y 4 B0 -3;V:>?@>B5W=C, ?V428ICT :>=F5=B@0FVN @8A?5@84>=C C ?;072V. 0;0=B0=575?V;  
=5 28O2;ONBL ;;V=VG=> 7=0GCI8E 5D5:BV2 =0 D0@<0:;>V=5B8:C @8A?5@84>=C B0 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW.  
\$5=>BV078=8, B@8F8:;VG=V 0=B845?@5A0=B8 B0 450:V β-1;:>0B>@8 <>6CBL ?V428IC20B8  
:>=F5=B@0FVN @8A?5@84>=C 2 ?;072V, 0;5 =5 :>=F5=B@0FVN 0=B8?A8E>B8G=>W D@0:FVW  
4=>G0A=5 70AB>AC20==O 8A?>;5?BC® ?5@>@0;L=> 7 ?0;V?5@84>=>< =5 @5:><5=4CTBLAO,  
>A:V;L:8 ?0;V?5@84>= T 0:B82=8< <5B01>;VB>< @8A?5@84>=C V WE :><1V=0FVO <>65 ?@8725AB8  
4> 4>40B:>2>3> 2?;82C 0:B82=>W 0=B8?A8E>B8G=>W D@0:FVW.  
;V=VG=5 4>A;V465==O 70 CG0ABN 13 ?0FVT=BV2 ?@>45<=>AB@C20;>, I> D0@<0:;>V=5B8G=V  
?>;07=8:8 ;VBN 7=0G=> =5 7 =59@>;5?B8:; I> 70AB>A>2CTBLAO >4=>G0A=>, 70;5?B><® C 4>7V 3  
<3 420 @078 =0 4>1C. !C=C 7 ;VBT< =5 4>A;V46C20;0AO. @8 >4=>G0A=>AC20==V =59@>;5?B8:V2  
B0 ;VBN A?>AB5@V30;8AO 28?04:8 5:AB@0?V@0 @>7;04V2 B0 7;>O:VA=>3> =59@>;5?B8G=>3>  
A8=4@>A;V465=L 1V;LH G0AB> ?>2V4<;O;>AO ?@> 28?04:8 5:AB@0?V@07;04V2 B0  
3V?5@:V=57VW ?@8 70AB>AC20==V ;VBN 7 =59@>;5?B8:0<8, =V6 >:@5< ;VBN.  
8A?>;5?B® =5 G8=8BL ;;V=VG=> 7=0G8<8E 5D5:BV2 =0 D0@<0:;>V=5B8:C,  
20;L?@>0BC, 483>:A8=C 01> B>?V@0<0BC.  
;>=075?0<, 3010?5=B8=, ;0<>B@8468=, <5B8;D5=V40B. 2060NG8 =0 D0@<0:;>V=5B8:C @8A?5@84>=C  
B0 707=0G5=8E 4VNG8E @5G>28= 270T<>4VW  
878:8 70AB>AC20==O 8A?>;5?BC® >4=>G0A=> 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 A8AB5<0B8G=> =5  
282G0;8AO. "5>@5B8G=> <>6;82V 270T<>4VW 7 CAV<0 0:B82=8<8 @5G>28=0<8, O:V G8=OBL 4VN =0  
F5=B@0;L=C =5@2>2C A8AB5:8 =5<0T 40=8E 4>40B:>28E 4>A;V465=L, A;V4 1CB8 >15@56=8<8 ?@8  
?@87=0G5==V @8A?5@84>=C >4=>G0A=> 7 V=H8<8 ;V:0@AL:8<8 70A>10<8.  
=D>@<0FVN I>4> ?V428I5=>W A<5@B=>ABV ?@8 >4=>G0A=>AC20==V 7 DC@>A5< C ?0FVT=BV2  
;VB=L>3> 2V:C 7 45<5=FVTN 482. C @>74V;V «A>1;82>ABV 70AB>AC20==O».

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

\$0@<0:>48=0

8A?5@84>= F5 A5;5:B82=89 <>=>0=VAB 7 C=V:0;L=8<8 2;0AB82>ABO<8. V= 28O2;OT 28A>:C  
0DV==VABL I>4> A5@>B>=V=5@3VG=8E 5-" V 4>D0D2-@5F5?B>@V2. 8A?5@84>= 72O7CTBLAO  
B0:>6 7 α<sub>1</sub>-04@5=5@3VG=8<8 @5F5?B>@0<8 B0 7 <5=H>N 0DV==VABN - 7<sub>1</sub>-3VAB0α<sub>2</sub>-  
04@5=5@3VG=8<8 @5F5?B>@0<8. 8A?5@84>= =5 28O2;OT 0DV==>ABV 2V4=>A=> E>;V=5@3VG=8E  
@5F5?B>@V2. %>G0 @8A?5@84>= T ?>BC6=8< D2-0=B03>=VAB<, I> ?>2O7CNBL 7 9>3>  
5D5:B82=VABN I>4> ?@>4C:B82=>W A8<0B8:8 H87>D@5=VW, 2V= =5 A?@8G8=OT 7=0G=>3>  
?@83=VG5==O <>B>@=>W 0:B82=>ABV B0 <5=H>N N V=4C:CT :0B0;5?AVN ?>@V2=O=> 7 ;;0A8G=8  
<8 =59@>;5?B8:0<8. 10;0=A>20=89 F5=B@0;L=89 0=B03>=V7< 2V4=>A=> A5@>B>=V=C B0 4>D0  
1VG=8E 5D5:BV2 V @>7H8@NT B5@0?52B8G=89 2?;82 ?@5?0@0BC 7 >E?>;5==O< =530B82=8E B0  
0D5:B82=8E A8D@5=VW.

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

8A?>;5?B® C D>@.; I> 48A?5@3CNBLAO C @>B>2V9 ?>@>6=8=V, B0 @>7G8= 4;O ?5@>@0;L=>3>  
70AB>AC20==O T 1V>5:2V20;5=B=8<8 4> B01;5B>;, 2:@8B8E >1>;>=:>N.

8A?5@84>= <5B01>;V7CTBLAO 4> 9-3V4@>:A8@8?5@84>=C, O:89 <0T ?>4V1=C 4> @8A?5@84>=C  
D0@<0:;>;3VG=C 4VN (482. @>74V; «□V>B@0=AD>@<0FVO B0 5;V).

A<>:BC20==O

VA;O ?5@>@0;L=>3> ?@89> ?>2=VABN 01A>@1CTBLAO B0 4>AO30T ?V:>28E :>=F5=B@0FV9 C  
?;07= <>6=0 ?@87=0G0B8 =570;56=> 2V4 ?@89>206=0 :>=F5=B@0FVO @8A?5@84>=C 2 >@30=V7ABV  
?0FVT=BV2 4>AO30TBLAO ?@>BO3>< 1 4=O. V2=>206=0 :>=F5=B@0FVO 9-3V4@>:A8@8A?5@84>=C  
4>AO30TBLAO ?@>BO3>< 4-5 4V1.

>7?>4V;

8A?5@84>= H284:> @>7?>4V;OTBLAO 2 >@30=V7= 72O7CTBLAO 7 0;L1C< V :8A;8< α<sub>1</sub>-  
3;V:>?@>B5W=>= =0 90 % 72O7CTBLAO 7 1V;0<8 ?;07<8, 9-3V4@>:A8@8A?5@84>= =0 77 %.

V>B@0=AD>@<0FVO B0 282545==O

8A?5@84>= <5B01>;V7CTBLAO F8B>E@><< CYP2D6 4> 9-3V4@>:A8@8A?5@84>=C, O:89 G8=8BL  
0=0;>3VG=C @8A?5@84>=C D0@<0:>;>3VG=C 4VN. 8A?5@84>= V 9-3V4@>:A8@8A?5@84>=  
CB2>@NNBL 0:B82=C 0=B8?A8E>B8G=C D@0:FVN. &8B>E@< CYP2D6 ?V440TBLAO 35=5B8G=>;V  
<>@DV74V1=0.

=H8< H;OE<< <5B01>;V7=C T N-4570;;V;C20==O. >A;V465==O *in vitro*=0 A><0E ?5GV=:8 ;N48=8  
>:070;8, I> @8A?5@84>= C ;;V=VG=> 7=0GCI8E :>=F5=B@0FVVOE =5 ?@83=VGCT 7=0G=> <5B01>;V7  
< ;V:0@AL:8E 70A>1V2, O:V <5B01>;V7CNBLAO V7>D5@<5=B0<8 F8B>E@>AC20==O ?@5?0@0BC  
70 % 4>78 282>48BLAO 7 A5G5N, 14 % 7 :0;> >=F5=B@0FVO @8A?5@84>=C V 9-  
3V4@>:A8@8A?5@84>=C C A5GV 4>@V2=NT 35-45 % ?@89=OB>W 4>78. =HC G0AB8=C AB0=>2;OBL  
=50:B82=V <5B01>;VB8. VA;O ?5@>@0;L=>3> ?@89>@8E =0 ?A8E>78 ?5@V>4 =0?V2282545==O  
AB0=>28BL ?@81;87=> 3 3>48=8. 5@V>4 =0?V2282545==O 9-3V4@>:A8@8A?5@84>=C B0 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW 4>AO30T 24 3>48=.

V=V9=VABL

>=F5=B@0FVW @8A?5@84>=C 2 ?;07?>@FV9=V 4>7V ?@5?0@0BC (2 <560E B5@0?52B8G=8E 4>7).  
0FVT=B8 ;VB=L>3> 2V:C B0 ?0FVT=B8 7 ?>@CH5==O<8 DC=:FVW =8@>;, ?5GV=:8  
>A;V465==O >4=>@07>2>3> ?@89> C A5@54=L=>F5=B@0FVW 0:B82=>W 0=B8?A8E>B8G=>W  
D@0:FVW C ?;072H89 ?5@V>4 =0?V2282545==O V 7=865==O ;;V@5=AC 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW =0 30 % C ?0FVT=BV2 ;VB=L>3> 2V:C. 8I0 :>=F5=B@0FVO 0:B82=>W  
0=B8?A8E>B8G=>W D@0:FVW C ?;07W 0=B8?A8E>B8G=>W D@0:FVW 2 A5@54=L>AB5@V30;8AO C  
?0FVT=BV2 7 =8@:>2>N =54>AB0B=VABN. # ?0FVT=BV2 7 ?5GV=:>2>N =54>AB0B=VABN  
A?>AB5@V30;8AL =>@<0;L=V @V2=V :>=F5=B@0FVW @8A?5@84>=C 2 ?;07W D@0:FVW  
@8A?5@84>=C C ?;07 71V;LH5=5 =0 35 %.

VB8

\$0@<0:>:V=5B8:0 @8A?5@84>=C, 9-3V4@>:A8@8A?5@84>=C B0 0:B82=>W 0=B8?A8E>B8G=>W  
D@0:FVW C 4VB59 ?>4V1=0 4> B0:>W C 4>@>A;8E.

!B0BL, @0A>20 ?@8=0;56=VABL B0 :C@V==O

>?C;OFV9=89 D0@<0:>:V=5B8G=89 0=0;V7 =5 28O282 2848<>3> 2?;82C AB0BV, 2V:C G8 728G:8  
:C@8B8 =0 D0@<0:>:V=5B8:C @8A?5@84>=C G8 0:B82=>W 0=B8?A8E>B8G=>W D@0:FVW.

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

A=>2=V DV78:>-EVABV: A2VB;>->@0=6520, 284>265=0, 42>>?C:;0, 2:@8B0 >1>;>=:>N B01;5B:0, 7  
=0?8A0<8 «Ris» V «2», @>74V;5=8<8 @>7?>4V;LG>N @8A:>N.

"5@ABV. 3 @>:8.

#<>28 715@V30==O.

15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B530 ! C =54>ABC?=>

#?0:>2:0.

> 10 B01;5B>;, 2:@8B8E >1>;>=:>N, C 1;VAB5@V V7 %//%/0;NW D>;L38, ?> 2 01> ?> 6 1;VAB5@V2 C  
:0@B>==V9 ?0GFV.

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

0 @5F5?B>

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

/=AA5=-!V;03 !?../Janssen Cilag S.p.A.

**VAF57=0E>465==O.**

V0 !/=AA5=, 04100 >@3> !0= VH5;L, 0BV=0, B0;VO/  
Via !. Janssen, 04100 Borgo S. Michele, Latina, Italy.