

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

(CONCOR®)

!;:04:

4VNG0 @5G>28=0: bisoprolol;

1 B01;5B:0

4>?>28=8: :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89, <03=VN AB50@0B, :@>A?>2V4>=, F5;N;>70

:@8AB0;VG=0, :@>E<0;L :C:C@C47O=89, :0;LNVN 3V4@>D>AD0B 1572>4=89;

?;V2:>20 >I>;>=:0 4;O B01;5B>: ?> 5 <3: 70;V70 >:A84 6>2B89 (172), 48<5B8:>= 100, <0:@>3>; 400, B8B0=C 4V>:A84 (171), 3V?@><5;>70 2910/15;

?;V2:>20 >I>;>=:0 4;O B01;5B>: ?> 10 <3: 70;V70 >:A84 6>2B89 (172), 70;V70 >:A84 G5@2>=89 (172), 48<5B8:>= 100, <0:@>3>; 400, B8B0=C 4V>:A84 (171), 3V?@><5;>70 2910/15.

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N.

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

B01;5B:8 5 <3: 6>2BC20B>-1V;V, A5@F5?>4V1=V, 42>>?C:;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 7 @8A:>N 7 >1>E 1>:V2;

B01;5B:8 10 <3: A2VB;>@<0=652V, A5@F5?>4V1=V, 42>>?C:;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 7 @8A:>N 7 >1>E 1>:V2.

\$0@<0:>B5@0?52B8G=0 3@C?0. !5;5:B82=V 1;>:0B>@8 15B0-04@5=>@5F5?B>@V2.

>4 "% !0707.

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

\$0@<0:>48=0VA>?@>;>; 28A>:>A5;5:B82=89 B1-04@5=>1;>:0B>@. 5 <0T 2=CB@VH=L>W A8

28@065=8E <5<1@0=>AB01V;V7CNG8E 2;0AB82>AB59. @5?0@0B <0T 4C65 =87L:C A?>@V4=5=VABL

V7 B2-@5F5?B>@0<8 3;04:>W =EV2 V AC48=, 0 B0:>6 V7 B2-@5F5?B>@0<8, O:V 15@CBL CG0ABL C

<5B01>;VG=V9 @53C;OFVW. "0:8< G8=><, 1VA>?@>;>; =5 2?;820T =0 >?V@ 48E0;L=8E H;OEV2 V B2-

>?>A5@54:>20=V <5B01>;VG=V 5D5:B8. !5;5:B82=VABL 1VA>?@>;>;C 2V4=>A=> B1-

04@5=>@5F5?B>@V2 ?>H8@NTBLAO 70 <56V B5@0?52B8G=>3> 4V0?07>=C 4>7.

VA>?@>;>; =5 <0T 28@065=>3> =530B82=>3> V=>B@?=>3> 5D5:BC.

0:A8<0;L=89 5D5:B 1VA>?@>;>;C =0ABC?0T G5@57 3-4 3>48=8 ?VA;O ?5@>@0;L=>3> ?@89>4

=0?V2282545==O 7 ?;07<8 A:;040T 10-12 3>48=, I> ?@872>48BL 4> 24-3>48==>W 5D5:B82=>ABV ?VA;O

>4=>@07>2>3> ?@89>

@8 V=B5=A82=V9 B5@0?VW C ?0FVT=BV2 7 VH5N E2>@>1>N A5@FO 157 E@>=VG=>W A5@F52>W

=54>AB0B=>ABV 1VA>?@>;>; 7<5=HCT A5@F5289 28:84 B0 ?>B@51C :0@40 2 :8A=V 7024O:8 7

<5=H5==N !! B0 C40@=>3> >1T?V@ 7<5=HCTBLAO. "0:>6 2 >A=>2V 0=B83V?5@B5=782=>3> 5D5:BC

B1-;>:0B>@V2 ;568BL<5E0=V7< 4VW 7=865==O 0:B82=>ABV @5=V=C 2 ?;07

VA>?@>;>; ?@83=VGCT @50:FVN =0 A804@5=5@3VG=C 0:B82=VABL, 1;>:CNG8 :0@4V>-B1-

@5F5?B>@8. &5 ?@872>48BL 4> C?>2V;L=5==O A5@F518BBO B0 7=865==O A:>@>GC20;L=>W

DC=:FVW :0@40, I> A?@8G8=OT 7=865==O ?>B@518 :0@40 2 :8A=V. 024O:8 FL>AO30TBLAO 1060=89

5D5:B C ?0FVT=BV2 7V AB5=>:0@4VTN B0 VH5N E2>@>1>N A5@FO.

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

IA>@1FVO. VA;O ?@89> 1V;LH =V6 90% 1VA>?@>;>;C 01A>@1CTBLAO 7V H;C=:>2>:8H:>2>3>

B@0:BC. 1A>@1FVO =5 70;568BL 2V4 ?@89>3> ?@>E>465==O AB0=>28BL ≤ 10 %. V>4>ABC?=VABL

AB0=>28BL 1;87L:> 90 %. >7?>4V;. 1T< @>7?>4V;C AB0=>28BL 3,5 ;/:3. 2O7C20==O 7 1V;:0<8 ?;07<8

:@>2V AB0=>28BL 1;87L:> 30 %.

5B01>;V7< B0 282545==O. VA>?@>;>; 282>48BLAO 7 >@30=V7<0 H;OE0<8: 50 % 1V>B@0=AD>@

@5==O< =50:B82=8E <5B01>;VBV2 B0 282>48BLAO =8@:0<8, 50 % 282>48BLAO =8@:0<8 C =57

?@>;>;C AB0=>28BL 15 ;/3>4. 024O:8 B@820;>4C =0?V2282545==O (10-12 3>48=) ?@5?0@0B 715@V30T

B5@0?52B8G=89 5D5:B 2?@>4>26 24 3>48= ?@8 70AB>AC20==V >48= @07 =0 4>1C.

V=V9=VABL. \$0@<0:>:V=5B8:0 1VA>?@>;>;C ;V=V9=0, WW ?>:07=8:8 =5 70;560BL 2V4 2V:C.

A>1;82V 3@C?8 ?0FVT=BV2. A:V;L:8 1VA>?@>;>; 282>48BLAO V7 >@30=V7@CH5==O< DC=:FVW

?5GV=:8 01> ?>@CH5==O< DC=:FVW =8@>: :>@5:FVO @5687C20==O =5 ?>B@V1=0. \$0@
<0:;>:V=5B8:0 C ?0FVT=V2 7V AB01V;L=>N E@>=VG=>N A5@F52>N =54>AB0B=VABN B0 7
?>@CH5==O< DC=:FV9 ?5GV=:8 01> =8@>: =5 282G0;0AO. # ?0FVT=V2 7V E@>=VG=>N A5@F52>N
=54>AB0B=VABN DC=:FV>=0;L=>3> ::0AC (70 NYHA) @V25=L 1VA>?@>;>;C 2 ?;0?V 28I89 B0
?5@V>4 =0?V2282545==O 4>2H89 ?>@V2=O=> 7V 74>@>28<8 4>1@>2>;LFO<8. 0:A8<0;L=0
:>=F5=B@0FVO C ?;072V 2 @V2=>206=>28BL 64+21 =3/<; ?@8 4>1>2V9 4>7V 10 <3 B0 ?5@V>4V
=0?V2282545==O 17+5 3>48=.

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

>:070==O.

- @B5@V0;L=0 3V?5@B5=7VO;
- VH5@>10 A5@FO (AB5=>:0@4VO);
- E@>=VG=0 A5@F520 =54>AB0B=VABL V7 A8AB>;VG=>N 48ADC=:FVTN ;V2>3> H;C=>G:0 C :>
<1V=0FVW 7 V=3V1VB>@0<8 \$, 4VC@5B8:0<8, C @07V =5>1EV4=>ABV A5@F528<8 3;V:>7840<8.

@>B8?>:070==O.

- >AB@0 A5@F520 =54>AB0B=VABL 01> A5@F520 =54>AB0B=VABL C AB0=V 45:~>B@51CT
V=>B@>?=>W B5@0?VW;
- :0@4V>35==89 H>;;
- 0B@V>25=B@8:C;O@=0 1;>:040 II V III ABC?5=O (70 28=OB:× B0:>W C ?0FVT=V2 7V HBCG=8<
2>4VT< @8B
- A8=4@>× A;01:>ABV A8=CA>2>3> 2C7;0;
- A8=>0B@V0;L=0 1;>:040;
- A8<0B8G=0 1@048:0@4VO;
- A8<0B8G=0 0@B5@V0;L=0 3V?>B5=7VO;
- B06:0 D>@<0 1@>=EV0;L=>W 0AB<8;
- ?V7=V AB04VW ?>@CH5==O ?5@8D5@8G=>3> :@>2>>1V3C 01> E2>@>18 59=>;
- D5>E@><>F8B><0, I> =5 ;V:C20;0AO;
- <5B01>;VG=89 0F84>7;
- ?V428I5=0 GCB;82VABL 4> 1VA>?@>;>;C 01> V=H8E :>5=V2 ?@5?0@0BC.

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

><1V=0FVW, O:V =5 @5:><5=4>20=> 70AB>A>2C20B8.

V:C20==O E@>=VG=>W A5@F52>W =54>AB0B=>ABV.

- =B80@8B18 ::0AC (=0?@8::04, EV=V48=, 487>?V@0:0W=, D5=VB>W=, D;5:0W=V4, ?@>?0D5=>=):
<>6;825 ?>B5=FVN20==O 5D5:BC I>4> 0B@V>25=B@8:C;O@=>W ?@>2V4=>ABV B0 ?>A8;5==O
=530B82=>3> V=>B@>?=>3> 5D5:BC.

AV ?>:070==O.

- =B03>=VAB8 :0;LFDVN (3@C?8 25@0?0N 48;BV075 =530B82=89 2?;82 =0 A:>@>GC20;L=C DC=:FVN
:0@40 B0 0B@V>25=B@8:C;O@=C ?@>2V4=VABL. =CB@VH=L>25==5 22545==O 25@0?0
- V?>B5=782=V ?@5?0@0B8 7 F5=B@0;L=8< <5E0=V7<< 4VW (:;>=V48=, <5B8;4>?0, <:>:Ao=V48=, @8;
<5=V48=): <>6;825 ?>3V@H5==O ?5@51V3C A5@F52>W =54>AB0B=>ABV 2=0A;V4>: 7=865==O
F5=B@0;L=>3> A83> B>=CAC (7=865==O G0AB>B8 A5@F528E A:>@>G5=L V A5@F52>3> 28:84C,
207>48;0B0FVO). 0?B>20 2V4A>1;82> O:I> 9>:0B>@V2 β -04@5=>@5F5?B>@V2, <>65 ?V428I8B8 @878:
28=8:=5==O @8:>H5B=>W 3V?5@B5=7VW.

><1V=0FVW, O:V A;V4 70AB>A>2C20B8 7 >15@56=VABN

V:C20==O 0@B5@V0;L=>W 3V?5@B5=7VW 01> VH5W E2>@>18 A5@FO (AB5=>:0@4VW).

- =B80@8B18 ::0AC (=0?@8::04, EV=V48=, 487>?V@0:0W=, D5=VB>W=, D;5:0W=V4, ?@>?0D5=>=):
<>6;825 ?>B5=FVN20==O 5D5:BC I>4> 0B@V>25=B@8:C;O@=>W ?@>2V4=>ABV B0 ?>A8;5==O
=530B82=>3> V=>B@>?=>3> 5D5:BC.

AV ?>:070==O.

- =B03=>VAB8 :0;LFDV B8?C 483V4@>?V@848=>2>3> @04C (=0?@8::04, =VD548?V=, D5;>48?V=, 0 <;>48?V=): <>6;825 ?V428I5==O @878:C 28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW. 5 28::;NG0TBLAO <>6;82VABL 7@>AB0==O =530B82=>3> 2?;82C =0 V=>B@>?>C DC=:FVN:0@40 C ?0FVT=BV2 V7 A5@F52>N =54>AB0B=VABN.
- =B80@8B40@>=): <>6;825 ?>B5=FVN20==O 2?;82C =0 0B@V>25=B@8:C;O@>C ?@>2V4=VABL.
- β-1;:>:0B>@8W 4VW (=0?@8::04, I> G=8E :@0?;OE 4;O ;V:C20==O 3;0C:<8): <>6;825 ?V4A8;5==O A8AB5<=8E 5D5:BV2 1VA>?@>;>;C.
- 0@0A8
- =AC;V= B0 ?5@>@0;L=V 3V?>3;V:518: ?V4A8;5==O 3V?>3;V:5W 4VW. ;:>:040 β-04@5=>@5F5?B>@V2 <>65 <0A:C20B8 A8<8 3V?>3;V:5
- 0A>18 4;O 0=5AB57VW: ?V428ICTBLAO @878: ?@83=VG5==O DC=:FVW :0@40 V 28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW (482. @>74V; «A>1;82>ABV 70AB>AC20==O»)).
- !5@F52V 3;V:>7848: 7=865==O G0AB>B8 A5@F528E A:>@>G5=L, 71V;LH5==O G0AC 0B@V>25=B@8:C;O@>=W ?@>2V4=>ABV.
- 5AB5@>W4=V ?@>B870?0;L=V 70A>18 () : <>6;825 ?>A;01;5==O 3V?>B5=782=>3> 5D5:BC 1VA>?@>;>;C.
- β-A8AC20==O C :<<1V=0FVW 7 ?@5?0@0B<< >=:>@ <>65 ?@8725AB8 4> 7=865==O B5@0?52B8G=>3> 5D5:BC >1>E 70A>1V2. ;O ;V:C20==O 0;5@3VG=8E @50:FV9 <>6CBL 1CB8 ?>B@V1=V 28IV 4>78 04@5=0;V=C.
- !8W :C;L302>ABV. >4V1=0 270T<>4VO 2V@>3V4=VH0 ?@8 70AB>AC20==V =5A5;5:B82=8E β- 1;:>:0B>@V2.
@8 ACAC20==V 7 0=B83V?5@B5=782=8<8 70A>10<8 B0 70A>10<8, I> 28O2;ONBL 3V?>B5=782=89 5D5:B (=0?@8::04, B@8F8::;VG=V 0=B845?@5A0=B8, 10@1VBC@0B8, D5=>BV078=) <>6;825 ?V428I5==O @878:C 0@B5@V0;L=>W 3V?>B5=7VW.
><1V=0FVW, I> <>6;82V.
- 5D;>EV=: <>6;825 ?V428I5==O @878:C @>728B:C 1@048:0@4VW.
- =3V1VB>@8 (70 28=OB:>< V=3V1VB>@V2 B8?C): ?V428I5==O 3V?>B5=782=>3> 5D5:BC β- 1;:>:0B>@V2, 0;5 T @878: @>728B:C 3V?5@B>=VG=>3> :@87C.

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

V:C20==O AB01V;L=>W E@>=VG=>W A5@F52>W =54>AB0B=>ABV V7 70AB>AC20==O 1VA>?@>;>;C A;V4 @>7?>G8=0B8 7 D078 B8B@C20==O.
0FVT=B0< V7 VH5N E2>@>1>N A5@FO ;V:C20==O =5 A;V4 ?@8?8=OB8 @0?B>2> 157 =030;L=>W ?>B@518, B> F5 <>65 ?@8725AB8 4> B@0=78B>@=>3> ?>3V@H5==O AB0=C. =VFN20==O B0 ?@8?8=5==O ;V:C20==O 1VA>?@>;>;< 28<030T @53C;O@=>3> <=>VB>@8=3C.
0 40=89 G0A =5<0T 4>AB0B=L>3> B5@0?52B8G=>3> 4>A2V4C ;V:C20==O A5@F52>W =54>AB0B=>ABV C ?0FVT=BV2 V7 =0ABC?>8<8 70E2>@N20==O<8 V ?0B>;>3VG=8<8 AB0=0<8: FC:@>289 4V015B B8?C (V=AC;V=>70;56=89), BO6:V ?>@CH5==O DC=:FVW =8@>:, BO6:V ?>@CH5==O DC=:FVW ?5GV=:8, @5AB@8:B82=0 :0@4V>?0BVO, 2@>465=V ?>@>:8 A5@FO, 35 <>48=0 7=0GCIV =01CBV ;:0?0==V 2048 A5@FO, V=D0@:B:0@40 ?@>BO3<< >AB0==VE 3 @5?0@0B A;V4 70AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0< ?@8 B0:8E AB0=0E:
- 1@>=E>A?07< (?@8 1@>=EV0;L=V9 0AB1AB@C:B82=8E 70E2>@N20==OE 48E0;L=8E H;OE2);
- FC:@>289 4V015B 7V 7=0G=8<8 :>;820==O<8 @V2=O 3;N:>78 2 :@>2V, ?@8 FL>
- AC2>@0 4VTB0;
- ?@>2545==O 45A5=A81V;V70FV9=>W B5@0?VW. /: V V=HVβ-1;:>:0B>@8, 1VA>?@>;>;<>65 ?V4A8;N20B8 GCB;82VABL 4> 0;5@35=V2 B0 71V;LHC20B8 206:VABL 0=0DV;0:B8G=8E @50:FV9 # B0:8E 28?04:0E ;V:C20==O 04@5=0;V=<=5 702648 40T ?>78B82=89 B5@0?52B8G=89 5D5:B;
- 0B@V>25=B@8:C;O@>=0 1;:>:040 I ABC?5=O;
- AB5=>:0@4VO @8=F<5B0;0;
- >1;VB5@CNGV 70E2>@N20==O ?5@8D5@8G=8E 0@B5@V9 (=0 ?>G0B:C B5@0?VW <>6;825 ?>A8;5==O A:0@3);
- 7030;L=0 0=5AB57VO.
?0FVT=BV2, O:8< ?;0=CTBLAO 7030;L=0 0=5AB57VO, 70AB>AC20==O β-1;:>:0B>@V2 7=86CT 28?04:8 0@8B:0@40 2?@>4>26 22545==O 2 =0@:>7, V=BC10FVW B0 ?VA;O>?5@0FV9=>3> ?5@V>4C. 5:<<5=4>20=> ?@>4>26C20B8 70AB>AC20==O β-1;:>:0B>@V2 ?V4 G0A ?5@8>?5@0FV9=>3>

?5@V>4C. 5>1EV4=> >1>2O7:>2> ?>?5@548B8 ;V:0@O=0=5AB57V>;>30 ?@> ?@89< 1;>:0B>@V2 B-04@5=>@5F5?B>@V2, >A:V;L:8 ;V:0@ ?>28=5= 2@0E>2C20B8 ?>B5=9V9=C 270T<>4VN 7 V=H8<8 ;V:0<8, O:0 <>65 ?@8725AB8 4> 1@04V0@8B@=>W B0EV:0@4VW B0 7=865==O <>6;82>AB59 @5D;5:B>@=>3> <5E0=V72>2B@0B8. # @07V 2V4?@>;>;C ?5@54 >?5@0B82=8<8 2B@CG0==O<8 4>7C A;V4 ?>ABC?>2> 7=878B8 B0 ?@8?8=8B8 ?@89>< ?@5?0@0BC 70 48 3>48= 4> 7030;L=>W 0=5AB57VW. <<1V=0FVW 1VA>?@>;>;C 7 0=B03>=VAB0<8 :0;LFFVN 3@C?8 25@0?0 48;BV075 572060NG8 =0 B5, I> :0@4V>A5;5:B82=V B-1;>:0B>@8 (B1) <0NBL <5=H89 2?;82 =0 DC=:FVN ;535=L ?>@V2=O=> V7 =5A5;5:B82=8<8 B-1;>:0B>@0<8, A;V4 C=8:0B8 WE 70AB>AC20==O, O: V 2AVE B-1;>:0B>@V2, ?@8 >1AB@C:B82=8E 70E2>@N20==OE 48E0;L=8E H;OEV2, O:I> =5<0T 203<<8E ?@8G8=4;O ?@>2545==O B5@0?VW. # @07V =5>1EV4=>ABV ?@5?0@0B >=:>@ A;V4 70AB>A>2C20B8 7 >15@56=VABN. # ?0FVT=BV2 V7 >1AB@C:B82=8<8 70E2>@N20==O<8 48E0;L=8E H;OEV2 ;V:C20==O 1VA>?@>;>;< A;V4 @>7?>G8=0B8 V7 =09=86G>W <>6;82>W 4>78 B0 A;V4 A?>AB5@V30B8 70 AB0=>< ?0FVT=BV2 I>4> 28=8:=5==O =>28E A8A8

@8 1@>=EV0;L=V9 0AB V=H8E E@>=VG=8E >1AB@C:B82=8E 70E2>@N20==OE ;535=L, I> <>6CBL 28;;8:0B8 A8<8, ?>:070=0 AC?CB=O B5@0?VO 1@>=E>48;0B0B>@0<8. # 45O:8E 28?04:0E =0 B;V ?@89>=EV0;L=>N 0AB<>N G5@57 ?V428I5==O @578AB5=B=>ABV 48E0;L=8E H;OEV2 <>6CBL ?>B@51C20B8 1V;LH 28A>:8E 4>7 B2-A8 %2>@8< =0 ?A>@V07 (C B.G. 2 0=0<=57V) B-1;>:0B>@8 (=0?@8;;04 1VA>?@>;>?) ?@87=0G0NBL ?VA;O @5B5;L=>3> A?V22V4=>H5==O :>@8ABL/@878:. 0FVT=B0< V7 D5>E@><>F8B><>N ?@87=0G0NBL ?@5?0@0B >=:>@ BV;L:8 ?VA;O ?@87=0G5==O B5@0?VW α-04@5=>1;>:0B>@0<8. !8<8 B8@5>B>:A8:>7C <>6CBL 1CB8 70<0A:>20=V =0 B;V ?@89> AC20==V ?@5?0@0BC >=:>@ <>65 2V478B82=89 @57C;LB0B ?@8 ?@>2545==V 4>?V=3 :>=B@>;N.

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

03VB=VABL. VA>?@>;>;<0T D0@<0:>;>3VG=V 2;0AB82>ABV, O:V <>6CBL A?@8G8=8B8 H:V4;8289 2?;82 =0 ?5@51V3 203VB=>ABV B0/01> @>728B>: ?>40/=>2>=0@>465=>3>. /: ?@028;>, B-04@5=>1;>:0B>@8 7<5=HCNBL ?;0F5=B0@=89 :@>2>BV.; I> <>65 A?@8G8=OB8 70B@8CB@>1=>3> @>728B:C, 2=CB@VH=L>CB@>1=C A<5@BL, <8<>2V;L=89 01>@B 01> ?5@54G0A=V ?>;>38. >6CBL @>728=CB8AO ?>1VG=V 5D5:B8 C ?>40 B0 =>2>=0@>465=>3> (=0?@8;;04, 3V?>3;V:5;V:C20==O B-1;>:0B>@0<8 =5>1EV4=5, 1060=>, I>1 F5 1C2 B1-A5;5:B82=89 04@5=>1;>:0B>@.

?5@V>4 203VB=>ABV ?@5?0@0B 70AB>A>2CNBL BV;L:8 B>4V, :>;8 >GV:C20=0 :>@8ABL 4;O <0B5@V ?5@528ICT ?>B5=9V9=89 @878: 4;O ?>40. 5>1EV4=> :>=B@>;N20B8 <0B>2>-?;0F5=B0@=89 :@>2>BV: B0 7@>AB0==O ?>40. # @07V H:V4;82>3> 2?;82C =0 ?5@51V3 203VB=>ABV 01> ?>V4 A;V4 @>73;O=CB8 <>6;82VABL 0;LB5@=0B82=>3> ;V:C20==O.

VA;O ?>;>3V2 =>2>=0@>465=89<0T 7=0E>48B8AO ?V4 @5B5;L=8< =03;04>

5@V>4 3>4C20==O 3@C44N. 0=8E I>4> 5:A:@5FVW 1VA>?@>;>;C C 3@C4=5<>;>: =5<0T, B><5=4CTBLAO 70AB>A>2C20B8 ?@5?0@0B >=:>@ ?V4 G0A 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.

E>4V 4>A;V465=L 70 CG0ABN ?0FVT=BV2 7 VH5N E2>@>1>N A5@FO ?@5?0@0B =5 2?;8202 =0 740B=VABL :5@C20B8 02B><>1V;54=0: 2 V=482V4C0;L=8E 28?04:0E ?@5?0@0B <>65 2?;8=CB8 =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> ?@0FN20B8 7V A;;04=8<8 <5E0=V7<0<8. A>1;82C C203C =5>1EV4=> ?@84V;OB8 =0 ?>G0B:C ;V:C20==O, ?@8 778 ?@5?0@0BC 01> ?@8 270T<>4VW 7 0;>3>;5<.

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

@5?0@0B >=:>@ A;V4 ?@89<0B8 =5 @>76>2CNG8, 2@0=FV =0BI5, ?V4 G0A 01> ?VA;O A=V40=:C, 70?820NG8 =525;8:>N :V;L:VABN @V48=8.

@B5@V0;L=0 3V?5@B5=7VO; VH5@>10 A5@FO (AB5=>:0@4VO).

V:C20==O A;V4 @>7?>G8=0B8 ?>ABC?>2> 7 =87L:8E 4>7 V7 ?>40;LH8< ?V428I5==O< 4>78. 5:><5=4>20=0 4>70 AB0=>28BL 5<3 (1 B01;5B:0 ?@5?0@0BC >=:>@ ?> 5 <3) =0 4>1C. @8 =5206:>;VG=89 B8A: 4> 105 << @B.AB.) ?V4E>48BL 4>70 2,5<3.

0=5>1EV4=>ABV 4>1>20 4>70 <>65 1CB8 ?V428I5=0 4> 10 <3 (1 B01;5B:0 ?@5?0@0BC >=:>@ ?> 10 <3)
=0 4>1C. >40;LH5 71V;LH5==O 4>78 28?@0240=5 ;8H5 C 28=OB:>28E 28?04:0E. 0:A8<0;L=0 @5:>
<5=4>20=0 4>70 AB0=>28BL 20 <3 =0 4>1C.
>@83C20==O 4>78 2AB0=>2;NNBLAO ;V:0@5< V=482V4C0;L=> 70;56=> 2V4 G0AB>B8 ?C;LAC B0
B5@0?52B8G=>W :>@8ABV.
%@>=VG=0 A5@F520 =54>AB0B=VABL V7 A8AB>;VG=>N 48ADC=:FVTN ;V2>3> H;C=>G:0 C :>
<1V=0FVW 7 V=3V1VB>@0<8 \$, 4VC@5B8:0<8, ?@8 =5>1EV4=>ABV A5@F528<8 3;V:>7840<8.
!B0=40@B=0 B5@0?VO E@>=VG=>W A5@F52>W =54>AB0B=>ABV: V=3V1VB>@8 \$ (01> 1;>:0B>@8
0=3V>B5=78=>28E @5F5?B>@V2 C @07V =5?5@5=>A8<>ABV V=3V1VB>@V2 \$), 1;>:0B>@8
β-04@5=>@5F5?B>@V2, 4VC@5B8:8 V, 70 =5>1EV4=>ABV, A5@F52V 3;V:>7848.
>=:>@ ?@87=0G0NBL 4;O ;V:C20==O ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN 157
>7=0: 703>AB@5==O.
"5@0?VN ?>28=5= ?@>2>48B8 ;V:0@ 7 4>A2V4< ;V:C20==O E@>=VG=>W A5@F52>W
=54>AB0B=>ABV.
V:C20==O AB01V;L=>W E@>=VG=>W A5@F52>W =54>AB0B=>ABV ?@5?0@0B< >=:>@
@>7?>G8=0TBLAO 2V4?>2V4=> 4> ?>40=>W =86G5 AE5<8 B8B@C20==O B0 <>65 :>@83C20B8AO
70;56=> 2V4 V=482V4C0;L=8E @50:FV9 >@30=V7
1,25 <3* 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C 2?@>4>26 1 B86=O, O:I> 4>1@5 ?5@5=>A8BLAO,
?V428I8B8 4>
2,5 <3* 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C 2?@>4>26 =0ABC?=>3> 1 B86=O, O:I> 4>1@5
?5@5=>A8BLAO, ?V428I8B8 4>
3,75 <3* 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C 2?@>4>26 =0ABC?=>3> 1 B86=O, O:I> 4>1@5
?5@5=>A8BLAO, ?V428I8B8 4>
5 <3 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C 2?@>4>26 =0ABC?=8E 4 B86=V2, O:I> 4>1@5
?5@5=>A8BLAO, ?V428I8B8 4>
7,5 <3 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C 2?@>4>26 =0ABC?=8E 4 B86=V2, O:I> 4>1@5
?5@5=>A8BLAO, ?V428I8B8 4>
10 <3 1VA>?@>;>;C DC<0@0BC 1 @07 =0 4>1C O: ?V4B@8
* 0?>G0B:C B5@0?VW E@>=VG=>W A5@F52>W =54>AB0B=>ABV @5:<5=4CTBLAO
70AB>A>2C20B8 >=:>@ >@, B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, ?> 2,5 <3.
0:A8<0;L=0 @5:<5=4>20=0 4>70 1VA>?@>;>;C DC<0@0BC AB0=>28BL 10 <3 1 @07 =0 4>1C.
@>B03>< D078 B8B@C20==O =5>1EV4=89 :>=B@>;L 70 =0ABC?=8<8 ?>:07=8:0<8 68BBT4VO;L=>ABV
(0@B5@V0;L=89 B8A.; G0AB>B0 A5@F528E A:>@>G5=L) V A8<0<8 ?@>3@5AC20==O A5@F52>W
=54>AB0B=>ABV. !8<8 <>6CBL @>72820B8AO 7 ?5@H>3> 4=O ?VA;O ?>G0B:C ;V:C20==O.
>48DV:0FVO ;V:C20==O
/I> <0:A8<0;L=0 @5:<5=4>20=0 4>70 ?>30=> ?5@5=>A8BLAO, <>6;825 ?>ABC?>25 7=865==O 4>78.
/I> ?V4 G0A D078 B8B@C20==O 01> ?VA;O =5W A?>AB5@V30TBLAO ?>ABC?>25 ?>3V@H5==O
A5@F52>W =54>AB0B=>ABV, @>72820TBLAO 0@B5@V0;L=0 3V?>B5=7VO 01> 1@048:0@4VO, @5:>
<5=4CTBLAO :>@83C20==O 4>78 ?@5?0@0BC, I> <>65 ?>B@51C20B8 B82>3> 7=865==O 4>78
1VA>?@>;>;C 01>, <>6;82>, ?@87C?8=5==O ;V:C20==O. VA;O AB01V;V70FVW AB0=C ?0FVT=B0
702648 A;V4 @>73;O40B8 <>6;82VABL ?>2B>@=>W V=VFV0FVW ;V:C20==O 1VA>?@>;>;>
5 A;V4 ?@8?8=OB8 ;V:C20==O ?@5?0@0B< @0?B>2>, >A>1;82> ?0FVT=B0< 7 VH5N E2>@>1>N
A5@FO, >A:V;L:8 F5 <>65 ?@8725AB8 4> ?>3V@H5==O AB0=C ?0FVT=B0. # @07V =5>1EV4=>ABV
;V:C20==O ?@5?0@0B< @5:<5=4>20=> 7025@HC20B8 ?>2V;L=>, ?>ABC?>2> 7=86CNG8 4>7C
(=0?@8:;04, 7<5=HCNG8 4>7C 242VGV I>B86=O).
V:C20==O AB01V;L=>W E@>=VG=>W A5@F52>W =54>AB0B=>ABV 70728G09 4>23>B@820;5.
C@A ;V:C20==O ?@5?0@0B< >=:>@ B@820;89 B0 70;568BL 2V4 ?@8@>48 B0 BO6:>ABV E2>@>18.
0FVT=B8 7 ?5GV=:>2>N B0/01> =8@:>2>N =54>AB0B=VABN.
@B5@V0;L=0 3V?5@B5=7VO; VH5@>10 A5@FO. ;O ?0FVT=BV2 V7 ?>@CH5==O< DC=:FV9 ?5GV=:8
01> =8@>; ;53:>3> V A5@54=L>3> ABC?5=O BO6:>ABV ?V41V@ 4>78 70728G09 @>18B8 =5
?>B@V1=>. 0FVT=B0< V7 BO6:>N D>@<>N =8@:>2>W =54>AB0B=>ABV (;V@5=A :@50B8=V=C
<5=H5 20 < ;/E2) V ?0FVT=B0< V7 BO6:>N D>@<>N ?5GV=:>2>W =54>AB0B=>ABV 4>70 =5 ?>28==O
?5@528IC20B8 4>1>2C 4>7C 10 <3 ?@5?0@0BC >=:>@. >1<565=V 40=V I>4> 70AB>AC20==O
1VA>?@>;>;C ?0FVT=B0< =0 4V0;V7V. 5>1EV4=>ABV 7

%@>=VG=0 A5@F520 =54>AB0B=VABL 5<0T 40=8E I>4> D0@<0:>:V=5B8:8 1VA>?@>;>;C C
?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN >4=>G0A=> 7 ?>@CH5==O<8 DC=:FVW
?5GV=:8 01>=8@>:, B>7C =5>1EV4=> 7 >15@56=VABN.
0FVT=B8 ;VB=L>3> 2V:C=5 ?>B@51CNBL :>@83C20==O 4>78.

VB8. ;V=VG=V 40=V I>4> 5D5:B82=>ABV V 157?5:8 70AB>AC20==O ?@5?0@0BC 4;O ;V:C20==O
4VB59 2V4ACB=V, B>A>2C20B8 ?@5?0@0B FV9 :0B53>@VW ?0FVT=BV2.

5@54>7C20==O.

!8<8.
@8 ?5@54>7C20==V (=0?@8:;04, 70AB>AC20==O 4>1>2>W 4>78 15 <3 70B-1;>:0B>@0<8 T
1@048:0@4VO, 0@B5@V0;L=0 3V?>B5=7VO, 3>AB@0 A5@F520 =54>AB0B=VABL, 3V?>3;V:5=E>A?07
<> 45:V;L:0 28?04:V2 ?5@54>7C20==O C ?0FVT=BV2 V7 0@B5@V0;L=>N 3V?5@B5=7VTN B0 /01> VH5
N E2>@>1>N A5@FO (<0:A8<0;L=0 4>70 2000 <3 1VA>?@>;>;C). V40@B5@V0;L=0 3V?>B5=7VO. #AV
?0FVT=B8 >4C60;8. A=CT H8@>:0 20@V015;L=VABL V=482V4C0;L=>W GCB;82>ABV 4>
>4=>:@0B=>W 28A>:>W 4>78 1VA>?@>;>;C, ?0FVT=B8 V7 A5@F52>N =54>AB0B=VABN<>6CBL
1CB8 1V;LH GCB;82V 4> ?@5?0@0BC. ">G8=0B8 7 ?>ABC?>28< 71V;LH5==O< 4>7C20==O (482.
@>74V; «!>AV1 70AB>AC20==O B0 4>78»).

V:C20==O.

@8 ?5@54>7C20==V ?@8?8=ONBL ;V:C20==O ?@5?0@0B< B0 ?@>2>4OBL ?V4B@8
@8 1@048:0@4VW: 2=CB@VH=L>25==5 22545==O 0B@>?V=C. !:I> @50:FVO 2V4ACB=O, 7
>15@56=VABN 22>4OBL V7?>@5=0;V= 01> V=H89 ?@5?0@0B V7 ?>78B82=8< E@>=>B@>?>=8<
5D5:B>28E 28?04:0E <>65 7=04>18B8AL B@0=A25=>7=5 22545==O HBCG=>3> 2>4VO @8B
@8 0@B5@V0;L=V9 3V?>B5=7VW: 2=CB@VH=L>25==5 22545==O @V48=8 B0 AC48=>72C6C20;L=8E
?@5?0@0BV2. =CB@VH=L>25==5 22545==O 3;N:03>=C <>65 1CB8 :>@8A=8
@8 0B@V>25=B@8:C;O@=V9 1;>:04V II V III ABC?5=O: @5B5;L=5 A?>AB5@565==O B0 V=DC7V9=5
22545==O V7?>@5=0;V=C 01> B@0=A25=>7=5 22545==O :0@4V>AB8@0.
@8 703>AB@5==V E@>=VG=>W A5@F52>W =54>AB0B=>ABV: 2=CB@VH=L>25==5 22545==O
4VC@5B8G=8E 70A>1V2, V=>B@>?>=8E ?@5?0@0BV2, 207>48;0B0B>@V2.
@8 1@>=E>A?07=E>;VB8G=V ?@5?0@0B8 (=0?@8:;04, V7?>@5=0;V=), B2-04@5=>DV;V=
@8 3V?>3;V:525==5 22545==O 3;N:>78.

>1VG=V @50:FVW.

51060=V 5D5:B8 70 G0AB>B>N 28=8:=5==O ::0A8DV:CNBL 70 B0:8<8 :0B53>@VO<8:
4C65 G0AB> (≥ 1/10), G0AB> (≥ 1/100 V < 1/10), =5G0AB> (≥ 1/1000 V < 1/100), @V4:> (≥ 1/10000 V < 1
/1000), 4C65 @V4:> (< 1/10000), =52V4<> (G0AB>B0 =5 287=0G5=0 70 40=8<8).

I>:C A5@FO.

C65 G0AB>: 1@048:0@4VO (C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN).
'0AB>: >7=0:8 ?>3V@H5==O A5@F52>W =54>AB0B=>ABV (C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N
=54>AB0B=VABN).

5G0AB>: ?>@CH5==O 0B@V>25=B@8:C;O@=>W ?@>2V4=>ABV, 1@048:0@4VO (C ?0FVT=BV2 7
0@B5@V0;L=>N 3V?5@B5=7VTN 01> VH5N E2>@>1>N A5@FO), >7=0:8 ?>3V@H5==O A5@F52>W
=54>AB0B=>ABV (C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN 01> VH5N E2>@>1>N A5@FO).

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

'0AB>: 70?0<>@>G5==O*, 3>;>2=89 1V;L*.

V4:>: AV=:>?5.

I>:C >@30=V2 7>@C.

V4:>: 7=865==O A;L>7>284V;5==O (B@510 2@0E>2C20B8 ?@8 =>AV==V :>=B0:B=8E ;V=7).

C65 @V4:>: :>=N=:B82VB.

I>:C >@30=V2 A;CEC.

V4:>: ?>3V@H5==O A;CEC.

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

5G0AB>: 1@>=E>A?07< C ?0FVT=BV2 V7 1@>=EV0;L=>N 0AB<>N 01> >1AB@C:B82=8<8
70E2>@N20==O<8 48E0;L=8E H;OEV2 2 0=0<=57V.

V4:>: 0;5@3VG=89 @8=VB.

I>:C B@02=>3> B@0:BC.

'0AB>: =C4>B0, 1;N20==O, 4V0@5O, 70?>@.

I>:C H:V@8 B0 A?>;CG=8E B:0=8=.

V4:>: @50:FVW 3V?5@GCB;82>ABV, 2;;NG0NG8 A25@1V6, ?>G5@2>=V==O, 28A8?0==O.

C65 @V4:>: 0;>?5FVO. @8 ;V:C20==V B-1;>:0B>@0<8 <65 A?>AB5@V30B8AL ?>3V@H5==O AB0=C E2>@8E =0 ?A>@V07 C 283;04V ?A>@V0B8G=>3> 28A8?0==O.

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

5G0AB>: <O7>20 A;01:VABL, AC4<8.

I>:C ?5GV=:8.

V4:>: 35?0B8B.

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

'0AB>: 2V4GCBBO E>;>4C 01> >=VB5=7VO (C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN).

5G0AB>: >@B>AB0B8G=0 3V?>B5=7VO (C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN), 0@B5@V0;L=0 3V?>B5=7VO (C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN 01> VH5N E2>@>1>N A5@FO).

I>:C @5?@>4C:B82=>W A8AB5<8.

V4:>: ?>@CH5==O ?>B5=FWW.

A8EVG=V @>7;048.

5G0AB>: 45?@5AVO, ?>@CH5==O A=C.

V4:>: =VG=V :>H<0@8, 30;NF8=0FVW.

01>@0B>@=V ?>:07=8:8.

V4:>: ?V428I5==O @V2=O B@83;VF5@84V2 C :@>2V, ?V428I5==O 0:B82=>ABV ?5GV=:>28E D5@ <5=BV2 C ?;072V (!", ").

030;L=V @>7;048.

'0AB>: 0AB5=VO (C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN), 2B<;N20=VABL*.

5G0AB>: 0AB5=VO (C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN 01> VH5N E2>@>1>N A5@FO).

* !B>ACTBLAO BV;L:8 ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN 01> VH5N E2>@>1>N A5@FO. &V A8<8 70728G09 28=8:0NBL =0 ?>G0B:C B5@0?VW, A;01:> 28@065=V V 7=8:0NBL ?@>BO3< ?5@H8E 1-2 B86=V2.

@07V 28=8:=5==O ?>1VG=8E O28I 01> =51060=8E @50:FV9 =5>1EV4=> =5309=> ?@>V=D>@

"5@ABV. 5 @>:V2.

#<>28 715@V30==O. 15@V30B8 ?@8 B5ABC?=>

#?0:>2:0.> 30 B01;5B>: C 1;VAB5@V; ?> 1 1;VAB5@C C :0@B>==V9 :>@>1FV.

> 25 B01;5B>: C 1;VAB5@V; ?> 2 1;VAB5@8 C :0@B>==V9 :>@>1FV.

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

8@>1=8:. 5@: 0, V<5GG8=0 /Merck KGaA, Germany.

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.\$@0=:DC@B5@ (B@0AA5 250, 64293 0@