

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

(PRODEP)

!;:04:

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

1 :0?AC;0 :A5B8=C 3V4@>E;>@84C 5:2V20;5=B=> D;C>:A5B8=C 20 <3;

4>?>28=8: ;0:B>78 <>=>3V4@0B, :@>E<0;L :C:C@C47O=89, B0;L:, <03=VN AB50@0B, :@5<=VN

4V>:A84 :>;>W4=89 1572>4=89, =0B@VN :@>E<0;L3;V:>;OB (B8?);

65;0B8=>20 :0?AC;0 :A84 (E 171), 4V0<0=B>289 A8=V9 (E 133).

V:0@AL:0 D>@<0. □0?AC;8.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 2 7 A8=V< :>@?CA>< B0 A8=L>N :@8H5G:>N, 7

=0?8A>< «PRODEP» =02:>;> :>@?CAC H@8DB>< 1V;>3> :>;L>@C, =02:>;> :@8H5G:8 G>@=8<

H@8DB><; @>H>: 1V;>3> :>;L>@C.

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

=B845?@5A0=B8. >4 "X N06A B03.

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

\$0@<0:>48=0\$;C>:A5B8= 4VNG89 :>=5=B ?@5?0@0BC @>45? T 0=B845?@5A0=B>N AB@C:BC@>N

2V= =5 =0;560BL =V 4> B@8F8; ;VG=8E, =V 4> B5B@0F8; ;VG=8E 0=B845?@5A0=BV2. \$;C>:A5B8= <0T

7=0G=C 0=B845?@5A82=C 0:B82=VABL, I>, <01CBL, ?>2070=> 7 ?>BC6=8< A?5F8DVG=8<

V=3V1C20==O< 72>@>B=>3> 70E>?;5==O A5@>B>=V=C 2 A8=0?A0E =59@>=V2 F5=B@0;L=>W

=5@2>2>W A8AB5<8. \$;C>:A5B8=, =0 2V428E, 3VAB028E V 04@5=5@3VG=8E @5F5?B>@V2, ?@8 9>3>

70AB>AC20==V =5 A?>AB5@V30NBLAO =530B82=V O2810 7 1>:C A5@F52>-AC48==>W A8AB5<8, 0

B0:>6 V=HV O2810, 7C<>2;5=V 0=B8E>;V=5@3VG=>N 4VTN, E0@0:B5@=V 4;O B@8F8; ;VG=8E

0=B845?@5A0=BV2. 0=8E ?@> :0=F5@>35==C 01>

\$0@<0:>:V=5B8:0. \$;C>:A5B8= 4>1@5 2A<>:BCTBLAO ?@8 ?5@>@0;L=>4=>@07>2>

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

>:070==O.

>@>A;V

5;8:V 45?@5A82=V 5?V7>48/@>7;048.

02□O7;82>-<0=V0:0;L=V @>7;048.

5@2>20 1C;V :>W ?A8E>B5@0?VW 4;O 7<5=H5==O =5:>=B@>;L>20=>3> 26820==O W6V B0 7 <5B>N

>G8I5==O :8H5G=8:C.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> D;C>:A5B8=C 01> 4> 1C4L-O:8E V=H8E :>=5=BV2 ?@5?0@0BC. 4=>G0A=5

70AB>AC20==O 7 V=3V1VB>@0<8 (A5;5:B82=V, =5A5;5:B82=V), 2;:NG0NG8 ;V=57>;V4.

"O6:0 ?5GV=:>20 V =8@:>20 =54>AB0B=VABL, 5?V;5?AVO, AC4×=V AB0=8 2 0=0<=57V,

ACWF840;L=V 4C<0, 0B>=VO A5G>2>3> 1@>O:VA=0 3V?5@?;07VO ?5@542>W 70;>78.

@>: :

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

5@V>4 @V2 V ?>G0B:>< ;V:C20==O @>45?>< ?>28=5= AB0=>28B8 =5 <5=H5 14 4=V2. VA;O 2V445?C

4> ?>G0B:C B5@0?VW V=3V1VB>@0<8 ?>28==> ?@>9B8 =5 <5=H5 5 B86=V2. "O6:V, V=>4V 7 ;5B0;L=8

< :V=F5< @50:FVW (3V?5@B5@:;>=CA, 2535B0B82=0 =5AB01V;L=VABL, H284:V 707=8:V2 V

?>@CH5==O <>7:>28E DC=:FV9, 2;:NG0NG8 A8;L=5 71C465==O, 45;V@V9 V :>70AB>AC20==O

D;C>:A5B8=C 7 V=3V1VB>@0<8 ?@>B8?>:070=5 (482. @>74V; «@>B8?>:070==O»).

!;V4 1@0B8 4> C2038 B@820;89 ?5@V>4 =0?V2282545==O O: D;C>:A5B8=C, B0: V =>@D;C>:A5B8=C, ?@8 @>73;O4V D0@<0:>48=0

\$5=VB>W=.

@8 :><1V=>20=>AC20==V D;C>:A5B8=C B0 D5=VB>W=C 2V42V. 45O:8E 28?04:0E 28=8:0;8 ?@>O28 B>:A8G=>ABV. !;V4 B8B@C20B8 4>78 ?@5?0@0BV2 V :>=B@>;N20B8 ;;V=VG=89 AB0= ?0FVT=BV2. !5@>B>=V=5@3VG=V ;V:0@AL:V 70A>18. @8 >4=>G0A=>AC20==V 7 V=H8<8 A5@>B>=V=5@3VG=8 <8 ;V:0@AL:8<8 70A>10<8 (=0?@8::;04, B@0<04>;, B@8?B0=8) <>65 ?V428IC20B8AL @878: 28=8:=5==O A5@>B>=V=>2>3> A8=4@>AC20==O B@8?B0=V2 VA=CT ?V428I5=89 4>40B:>289 @878: 28=8:=5==O 207>:>=AB@8:FVW :>@>=0@=8E AC48= B0 3V?5@B5=7VW.

VBV9 V B@8?B>D0=. !;V4 70AB>A>2C20B8 7 >15@56=VABN D;C>:A5B8= 7 ;VBVT< G8 B@8?B>D0=> <, B0: O: 2V4B>=V=>2>3> A8=4@>4=>G0A=>AC20==V V=3V1VB>@V2 72>@>B=>3> 70E>?;5==O A5@>B>=V=C 7 40=8<8 ;V:0@AL:8<8 70A>10<8. @8 70AB>AC20==V D;C>:A5B8=C 7 ;VBVT< =5>1EV4=> G0ABVH5 :>=B@>;N20B8 ;;V=VG=89 AB0= ?0FVT=B0.

7>D5@<5=B CYP2D6. "0: O: <5B01>;V7< D;C>:A5B8=C (O: V B@8F8;;VG=8E 0=B845?@5A0=BV2 B0: V V=H8E A5;5:B82=8E A5@>B>=V=>28E 0=B845?@5A0=BV2) 2;;NG0TBLAO 2 A8AB5>3> F8B>E@> D5@<5=BC CYP2D6, >4=>G0A=5 70AB>AC20==O 7 ;V:0@AL:8<8 70A>10<8, I> B0:>6 <5B01>;V7CNBLAO F8<8 D5@<5=B0<8, <>65 ?@8725AB8 4> @50:FV9 270T<>4V9. ">(B0:V O: D;5:0V=V4, 5=:0V=V4, :0@10<075?V= V B@8F8;;VG=V 0=B845?@5A0=B8), A;V4 ?>G8=0B8 7 =09 <5=H8E 4>7, O:I> E2>@89 >4=>G0A=> >B@8:A5B8= 01> ?@89<02 9>3> ?@>BO3<< ?>?5@54=VE 5 B86=V2. # 28?04:C 2;;NG5==O D;C>:A5B8=C 2 @568< ;V:C20==O E2>@>3>, O:89 C65 ?@89<0T ?>4V1=89 ?@5?0@0B, A;V4 ?5@5410G8B8 7=865==O 4>78 ?5@H>3> ?@5?0@0BC.

;VB5@0BC@V ?>8AC20;0AL D0@<0:>:V=5B8G=0 270T<>4VO V=3V1VB>@V2 CYP2D6 V B0 <>:A8D5=C, 2V4AL 7=865==O =0 65-75% >4=>3> 7 1V;LH 0:B82=8E D>@< B0<>:A8D5=C, =0?@8::;04, 5=4>:A8D5=C. 45;V;L:>E 4>A;V465==OE 2V4 7=865==O 5D5:B82=>ABV B0<>:A8D5=C ?@8 >4=>G0A=>AC20==V 45O:8E V=3V1VB>@V2 72>@>B=>3> 70E>?;5==O A5@>B>=V=C. =865==O 5D5:B82=>ABV B0<>:A8D5=C =5 <>6=0 28;;NG8B8, B> <>6;82>ABV A;V4 C=8:0B8 >4=>G0A=>3> 70AB>AC20==O ?>BC6=8E V=3V1VB>@V2 CYP2D6, 2;;NG0NG8 D;C>:A5B8=, (482. @>74V; <<A>1;82>ABV 70AB>AC20==O»).

\$;C>:A5B8= <>65 ?>B5=FDV20B8 4VN 0;?@07>;0 WE A;V4 70AB>A>2C20B8 7 >15@56=VABN. @8 >4=>G0A=>AC20==V 7 D;C>:A5B8=>< 2V47=0G0TBLAO 7=F5=B@0FV9 C :@>2V ;;>70?V=C, 4V075?0;0 ?@>O28 B>:A8G=>W 4VW. @8 ?@89>:A5B8=C 7 2:070=8<8 ?@5?0@0B0<8 A;V4 ?5@53;O=CB8 :>=A5@20B82=89 ?V41V@ 4>78 ?@5?0@0BC V 74V9A=N20B8 :>=B@>;L AB0=C ?0FVT=B0.

\$;C>:A5B8= IV;L=> 7207CTBLAO 7 1V;;0<8 ?;07<8 :@>2V, B>:A5B8=C 7 V=H8< ?@5?0@0B<<, O:89 IV;L=> 7207CTBLAO 7 1V;;0<8 ?;07<8 :@>2V, <>6;82V 7=F5=B@0FV9 C ?;072V >1>E ?@5?0@0BV2. 5@>@0;L=V 0=B8:>03C;O=B8. @8 >4=>G0A=>AC20==V D;C>:A5B8=C 7 20@D0@8=>< 2V4AL 71V;LH5==O G0AC :@>2>B5GV.03C;O=B=>W 4VW (;01>@0B>@>V ?>:07=8:8 V/01> ;;V=VG=V >7=0:8 B0 A8<8) <0;8 =5?>ABV9=89 E0@0:B5@. !: C 28?04:C ;V:C20==O 20@D0@8=>< @07>< 7 V=H8<8 ?@5?0@0B0<8 4> ?>G0B:C 70AB>AC20==O 01> C 28?04:C ?@8?8=5==O ;V:C20==O D;C>:A5B8=C ?@8 B5@0?VW 20@D0@8=>< A;V4 ?@>25AB8 @5B5;L=89 :>=B@>;L ?>:07=8:V2 73>@B0==O :@>2V. @8 =5>1EV4=>ABV ?@87=0G5==O V=H8E ?@5?0@0BV2 ?VA;O 2V4:A5B8=C A;V4 2@0E>2C20B8 B@820;89 ?5@V>4 =0?V2282545==O D;C>:A5B8=C B0 9>3> 0:B82=>3> <5B01>;VBC =>@D;C>:A5B8=C V, 2 7207:C 7 F8<, <>6;82VABL @>728B:C ;V:0@AL:>W 270F>4VW (482. @>74V; <<A>1;82>ABV 70AB>AC20==O»).

;5:B@>?@>B8AC4><=0 B5@0?VO.

V4:> 2V4ABV =0?04V2 C E2>@8E, O:V ?@89<0NBL D;C>:A5B8=, ?@8 ?@>2545==V

5;5:B@>?@>B8AC4><=>W B5@0?VW. ">B@815@56=>ABV.

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

5 ?@>2>48;8AL D0@<0:>:V=5B8G=V V D0@<0:>48=0A;V465==O D;C>:A5B8=C 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, I> ?>4>26CNBL V=B5@20; QT. 448:B82=C 4VN D;C>:A5B8=C V 40=8E ;V:0@AL:8E 70A>1V2 =5 <>6=0 28;;NG8B8. "0:8< G8=><, A;V4 4>B@815@56=>ABV ?@8 >4=>G0A=>AC20==V D;C>:A5B8=C 7 ;V:0@AL:8<8 70A>10<8, I> ?>4>26CNBL V=B5@20; QT, B0:8<8 O: 0=B80@8B18 ;;0AC V, 0=B8?A8E>B8G=V ;V:0@AL:V 70A>18 (=0?@8::;04, ?>EV4=V D5=>BV07V=C, ?V<>784, 30;>?5@84>;), B@8F8;;VG=V 0=B845?@5A0=B8, 45O:V ?@>B81=V 70A>18 (=0?@8::;04, A?0@D;>:A0F8=, <>:A8D;>:A0F8=, 5@8B@>25==>3> 70AB>AC20==O, ?5=B0B8<0;O@V9=V ?@5?0@0B8, >A>1;82>

30;4>D0=B8=, 45O:V 0=B83VAB0, ;0AB8=).

::>3>;L.

V4 G0A ?@>2545==O 4>A;V465=L D;C>:A5B8= =5 ?V428IC202 @V25=L 0;:>3>;N 2 :@>2V V =5 ?>A8;N202 4VN 0;:>3>;N. @>B5 >4=>G0A=5 70AB>AC20==O V=3V1VB>@V2 72>@>B=>3> 70E>;5==O A5@>B=>V=C B0 0;:>3>;N =5 @5:>5=4CTBLAO.

2V@>1V9.

/: V 7 V=H8<8 V=3V1VB>@0<8 72>@>B=>3> 70E>;5==O A5@>B=>V=C, <>6CBL 28=8:0B8 D0@ <0:>48=0 ?@8 70AB>AC20==V ?@5?0@0BC V7

\$.C>:A5B8= ?>A8;NT 4VN FC:@>7=86C20;L=8E ?@5?0@0BV2.

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

(:V@=V 28A8?0==O B0 0;5@3VG=V @50:FVW.

@8 70AB>AC20==V D;C>:A5B8=C ?>2V4<;O;>AO ?@> 28?04:8 H:V@=8E 28A8?0=L, 0=0DV;0:B8G=8E @50:FV9 V ?@>3@5ACNG8E A8AB5<=8E ?>@CH5=L V7 70;CG5==O< C ?0B>;>3VG=89 ?@>F5A H:V@8, ;535=V2, ?5GV=:8. @8 ?>O2V H:V@=8E 28A8?V2 01> V=H8E 0;5@3VG=8E @50:FV9, 5BV>;>3VN O:8E =5 <>6=0 287=0G8B8, ?@89>< D;C>:A5B8=C A;V4 2V4

!C4><8.

@8 70AB>AC20==V 0=B845?@5A82=8E ;V:0@AL:8E 70A>1V2 VA=CT ?>B5=FV9=89 @878: 28=8:=5==O AC4>AC20==O D;C>:A5B8=C A;V4 ?@8?8=8B8 C ?0FVT=V2, 2 O:8E 28=8:;8 AC4<8 G8 VA=CT ?V428I5=89 @878: 28=8:=5==O AC4>AC20==O D;C>:A5B8=C C ?0FVT=V2 7 =5AB01V;L=8<8 AC4<8 <8 @>7;040<8/5?V;5?AVTN.

0=VO.

=B845?@5A0=B8 A;V4 7 >15@56=VABN 70AB>A>2C20B8 C ?0FVT=V2 7<0=VTN G8 3V?><0=VTN.

!;V4 ?@8?8=8B8 70AB>AC20==O D;C>:A5B8=C C ?0FVT=V2 7<0=V0:0;L=>N D07>N.

\$.C=:FVO ?5GV=:8/=8@>:.

\$.C>:A5B8= 0:B82=> <5B01>;V7CTBLAO 2 ?5GV=FV V 282>48BLAO =8@:0<8. 87L:V 4>78 O: 0;LB5@=0B82=V 4>1>2V 4>78 @5:>5=4>20=> ?0FVT=B0< 7 ?>@CH5==O< ?5GV=:8. @8 ?@89>2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C < 10<;E2) V ?0FVT=V2, O:V ?>B@51CNBL 35<>4V0;V7C, @V2=V C ?;07:A5B8=C G8 =>@D;C>:A5B8=C B0:V, O: C ?0FVT=V2 7 =>@<0;L=>N DC=:FVTN =8@>: @>B8?>:070=> 70AB>A>2C20B8 ?@8 B06:V9 ?5GV=:>2V9 B0 =8@:>2V9 =54>AB0B=>ABV.

"0<>:A8D5=.

0AB>AC20==O D;C>:A5B8=C, ?>BC6=>3> V=3V1VB>@0 CYP2D6 <>65 ?@872>48B8 4> 7=865==O :>=F5=B@0FVW 5=4>:A8D5=C, >4=>3> 7 =09206;82VH8E 0:B82=8E <5B01>;V2V2 B0<>:A8D5=C. "0:8< G8=><, ?> <>6;82>ABV A;V4 C=8:0B8 >4=>G0A=>3> B0<>:A8D5=C B0 D;C>:A5B8=C.

!5@F52>-AC48==V @>7;048.

?VA;O@5TAB@0FV9=>4V ?>2V4<;O;8AL 28?04:8 ?>4>265==O V=B5@20;C QT V H;C=>G:>2>W 0@8B (482 @>74V;8 <70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9», «>1VG=V @50:FVW», «5@54>7C20==O»).

!;V4 7 >15@56=VABN 70AB>A>2C20B8 C ?0FVT=V2 7 B0:8<8 AB0=0<8, O: 2@>465=89 ?>4>265=89 V=B5@20; QT, =0O2=VABL 2 0=0<=57V ?>4>265==O V=B5@20;C QT G8 V=H8E ;;V=VG=8E AB0=V2, I> <>6CBL ?@872>48B8 4> 0@8B:0;VT<03=VTAB@89 V=D0@:B :0@4C G8 45:>20=0 A5@F520 =54>AB0B=VABL) G8 C 28?04:C ?V428I5==O :>=F5=B@0FVW D;C>:A5B8=C (=0?@8:;04, ?5GV=:>20 =54>AB0B=VABL). 5@54 ?>G0B:> 70AB>AC20==O D;C>:A5B8=C =5>1EV4=> ?@>25AB8 .

/:I> ?V4 G0A ;V:C20==O D;C>:A5B8=> 28=8:0NBL A8<8 A5@F52>W 0@8B< D;C>:A5B8=C V ?@>25AB8 4>A;V465==O.

B@0B0 <0A8 BV;0.

?0FVT=V2, O:V ?@89<0NBL D;C>:A5B8=, <>65 2V4

&C:@>289 4V015B.

E2>@8E =0 FC:@>289 4V015B ?V4 G0A ;V:C20==O D;C>:A5B8=> 2V47=0G0;8AO 778 2 :@>2V. V?>3;V:5B03<< ;V:C20==O D;C>:A5B8=>, 0 ?VA;O 2V4G0B:C V ?VA;O 70:V=G5==O ;V:C20==O D;C>:A5B8=> <>65 ?>B@51C20B8AO :>@5:FVO 4>7 V=AC;V=C B0/01> 3V?>3;V:5.

!CWF84/ACWF840;L=V 4C3V@H5==O.

5?@5AVO ?>2O70=0 V7 7@>AB0==O< @878:C ACWF840;L=8E 4C<>., A?@>18 ACWF84C. 878: VA=CT
4>B8, ?>:8 =5 =0AB0T ?52=0 @5:@0I5==O <>65 =5 =0AB020B8 ?@>BO3<< :V;L:>E 01> 1V;LH5 B86=V2
;V:C20==O, 70 ?0FVT=B0<8 A;V4 C206=> A?>AB5@V30B8 4>B8, 4>:8 =5 =0AB0=5 ?>:@0I5==O.
030;L=89 ;V=VG=89 4>A2V4 ?>:07CT, I> @878: ACWF84C <>65 7@>AB0B8 =0 @0==VE AB04VOE
>4C60==O.

5>1EV4=> ?>ABV9=> A?>AB5@V30B8 70 ?0FVT=B0<8 7 25;8:8<8 45?@5A82=8<8 @>7;040<8 B0 V=H8
<8 ?A8EVG=8<8 70E2>@N20==O<8, B0: O: <>6;8289 @>728B>: V=H8E ?A8EVG=8E @>7;04V2.

!;V4 C206=> A?>AB5@V30B8 70 ?0FVT=B0<8, >A>1;82> 7 28A>:8< @878:<< @>728B:C ACWF840;L=8E
V459 G8 A?@>1, >A>1;82> =0 ?>G0B:C ;V:C20==O G8 ?@8 778. @>B8?>:070=> 70AB>A>2C20B8 C
?0FVT=BV2 7 ACWF840;L=8<8 4C

5B00=0;V7 ?;0F51>.->=B@>;L>20=8E 4>A;V465=L 70AB>AC20==O 0=B845?@5A82=8E ?@5?0@0BV2
4>@>A;8< ?0FVT=B0< V7 ?A8EVG=8<8 @>7;040<8 ?>:07CT 7@>AB0==O @878:C ACWF840;L=>W
?>254V=:8 C ?0FVT=BV2 2V:<< 4> 25 @>:V2, O:V ?@89<0NBL 0=B845?@5A0=B8, ?>@V2=O=> 7
?;0F51>.

@8 ?>O2V ;V=VG=>3> ?>3V@H5==O, ACWF840;L=8E A?@>1 G8 7254V=:8 A;V4 268B8 2V4?>2V4=8E
70E>4V2.

:0B87VO/?A8E><>B>@=0 48AD>@VO. 0AB>AC20==O D;C>:A5B8=C ?>2O70=> 7 @>728B:<<
0:0B87VW, O:0 AC1T:B82=> E0@0:B5@87CTBLAO =5>1EV4=VABN @CE0B8AO, G0AB> 7 =5
<>6;82VABN AB>OB8 01> A84VB8. &5 >A>1;82> 2V4

!8<8 2V4

'0AB> 28=8:0NBL A8<8 2V4 ;V:C20==O @0?B>2> ?@8?8=OTBLAO (482. @>74V; <<>1VG=V @50:FVW).
V4 G0A ;V=VG=8E 4>A;V465=L ?>1VG=V @50:FVW ?@8 ?@8?8=5==V ?@89>C 60 % ?0FVT=BV2,
?@8G>E D0:B>@V2, 2;;NG0NG8 B@820;VABL ;V:C20==O, 4>7C B0 @V25=L 7=865==O 4>78. !;V4
?@>2>48B8 B8B@C20==O 7<5=H5==O 4>78 ?@>BO3<< 1 G8 2 B86=V2 2V4?>2V4=> 4> ?>B@518
?0FVT=B0.

!8<8 2V43> G8 A5@54=L>3> ABC?5=O BO6:>ABV, 0;5<>6CBL 1VB8 V BO6:>3> ABC?5=O BO6:>ABV.
28G09=> 28=8:0NBL ?@>BO3<< ?5@H8E 4=V2 ?VA;O ?@8?8=5==O 70AB>AC20==O D;C>:A5B8=C.
0728G09 A8<8 A0<>ABV9=> <8=0NBL ?@>BO3<< ?5@H8E 2 B86=V2, E>G0 2 450:8E 28?04:0E <>6CBL
B@820B8 2-3 2H5. "0:8< G8=><, @5:><5=4>20=> ?>ABC?>2> 7=86C20B8 4>7C D;C>:A5B8=C ?@>BO3<
< I>=09<5=H5 1-2 B86=V2 2V4?>2V4=> 4> ?>B@51 ?0FVT=B0.

@>2>B5GV.

>2V4<<;O;>AO ?@> 28=8:=5==O ?V4H:V@=8E :@>2>28;82V2, B0:8E O: 5:EV<>78 G8 ?C@?C@0. :EV
<>78 28=8:0NBL @V4:> ?@8 ;V:C20==V D;C>:A5B8=>

V4@V07.

A=CNBL ?>2V4<<;5==O ?@> 28=8:=5==O ?@89<0;8 D;C>:A5B8=. "> A;V4 4>B@815@56=>ABV C
?0FVT=BV2 7 ?V428I5=8< 2=CB@VH=L->->G=8< B8A:>< G8 @878:<< 28=8:=5==O 3>AB@>W 70:@8B>-
:CB>2>W 3;0C:><8. @>B8?>:070=> 70AB>A>2C20B8 C ?0FVT=BV2 7 3;0C:><>N.

;5:B@?>@>B8AC4><=0 B5@0?VO.

V4:> 2V4ABV =0?04V2 C E2>@8E, O:V ?@89<0NBL D;C>:A5B8=, ?@8 ?@>2545==V

5;5:B@?>@>B8AC4><=>W B5@0?VW. ">B@815@56=>ABV.

2V@>1V9.

@8 >4=>G0A=>AC20==V D;C>:A5B8=C B0 72V@>1>N ?V428ICTBLAO @878: 28=8:=5==O
A5@>B>=V=5@3VG=8E 5D5:BV2, B0:8E O: A5@>B>=V=>289 A8=4@<, I> <>65 28=8:0B8 ?@8
70AB>AC20==V V=3V1VB>@V2 72>@>B=>3> 70E>?;5==O A5@>B>=V=C B0 @>A;8==8E
?@5?0@0BV2, I> 1V9.

V4:V 28?04:8 @>728B:C A5@>B>=V=>2>3> A8=4@>O:VA=>3> =59@>;5?B8G=>3> A8=4@>2V4>
<<O;>AL C ?0FVT=BV2 ?@8 ?@89>:A5B8=C, >A>1;82> 2 :<<1V=0FVW 7 V=H8<8

A5@>B>=V=5@3VG=8<8 (A5@54 V=H8E L-B@8?B>D0=) V/G8 =59@>;5?B8G=8E ;V:0@AL:8E
70A>1V2. "0: O: FV A8<8 <>6CBL 1CB8 68BBT2> =5157?5G=8<8, ;V:C20==O D;C>:A5B8=<< A;V4
?@8?8=8B8 V 70157?5G8B8 ?V4B@8;=>CA, =5AB01V;L=VABL 2535B0B82=>W =5@2>2>W A8AB5<8 7
<>6;828<8 ?>@CH5==O<8 68BBT2>-206;828E DC=:FV9, ?A8EVG=>3> AB0BCAC, 2;;NG0NG8
?>@CH5==O A2V4><>ABV, ?>4@07;82VABL, ?@>3@5ACNGC 068B0FVN 06 4> 45;V@VN V :>
@8 70AB>AC20==V D;C>:A5B8=C <>6;8289 @>728B>: 3V?>=0B@VTA=>2=> 4;O ?0FVT=BV2
;VB=L>3> 2V:C B0 E2>@8E, O:V >45@6CNBL 4VC@5B8:8, 2=0A;V4>: 7<5=H5==O &.

@5?0@0B 7C, B>3> =5 A;V4 70AB>A>2C20B8 ?0FVT=B0< V7 B0:8<8 @V4:VA=8<8 A?04:>28<8
?>@CH5==O<8, O: =5?5@5=>A878, 2@>465=0 =54>AB0B=VABL ;0:B078 01> A8=4@<3;N:>7->
30;0:B>7=>W <0;L01A>@1FVW.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.
@>B8?>:070=>.

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

V4 G0A ;V:C20==O @>45?< A;V4 CB@8B@0=A?>@B< 01> @>1>B8 7 V=H8<8 <5E0=V7<0<8.

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

5:8:V 45?@5A82=V 5?V7>48/@>7;048.

>G8=0B8 B5@0?VN @>45?< =5>1EV4=> 7 20 <3 =0 4>1C 70 >48= @0=:>289 ?@89><, B0:0 4>70
4>AB0B=O 4;O 4>AO3=5==O 0=B845?@5A82=>3> 5D5:BC. # @07V ;V=VG=>W =5>1EV4=>ABV
G5@57 3-4 B86=V 2V4 ?>G0B:C B5@0?VW 4>7C <>6=0 71V;LH8B8 4> 20 <3 42VGV =0 4>1C; E>G0
71V;LH5==O 4>78 ?@872>48BL 4> ?>B5=FBV9=>3> 7@>AB0==O ?>1VG=8E 5D5:BV2, 45O:8< ?0FVT=B0
< V7 =54>AB0B=L>N 2V4?>2V44N =0 ;V:C20==O 4>7>N 20 <3, 4>7C <>6=0 ?>ABC?>2> 71V;LH8B8 4>
60 <3 =0 4>1C. >7C 71V;LHCNBL V=482V4C0;L=> B0 7 >15@56=VABN, B5@0?VN A;V4 @>7?>G8=0B8
7

0FVT=B8 7 45?@5A82=8<8 @>7;040<8 ?>28==V ;V:C20B8AO ?@>BO3< 4>AB0B=L>3> G0AC, I=>09
<5=H5 ?@>BO3>< 6 ABV A8@N20==O.

02□07;82>-<0=V0:0;L=V @>7;048.

28G09=0 @5:><5=4>20=0 4>70 AB0=>28BL 20 <3 =0 4>1C. %>G0 71V;LH5==O 4>78 ?@872>48BL 4>
>?>B5=FBV9=>3> 7@>AB0==O ?>1VG=8E 5D5:BV2, 45O:8< ?0FVT=B0< V7 =54>AB0B=L>N 2V4?>2V44N
=0 ;V:C20==O ?@>BO3< 2 B86=V2 4>7>N 20 <3, 4>7C <>6=0 ?>ABC?>2> 71V;LH8B8 4> 60 <3 =0 4>1C.
/:I ?@>BO3>< 10 B86=V2 ;V:C20==O 2V4ACB=V9 ;V=VG=89 5D5:B, B5@0?VN D;C>:A5B8=< A;V4
?5@53;O=CB8. /:I> 1C;> >B@8<0=> ?>78B82=89 B5@0?52B8G=89 5D5:B 2V4 ;V:C20==O, A;V4
?@>4>268B8 B5@0?VN D;C>:A5B8=< 70 V=482V4C0;L=> ?V4V1@0=>N 4>7>N ?@5?0@0BC. >7C
71V;LHCNBL V=482V4C0;L=> B0 7 >15@56=VABN, B5@0?VN ?>B@V1=> ?@>2>48B8N 4>7>N.
5@V>48G=> A;V4 ?5@53;O40B8 ?>B@51C E2>@>3> 2 ;V:C20==V ?@5?0@0B>2>48B8 AC?CB=N
?A8E>B5@0?VN ?0FVT=B0< V7 4>AB0B=L>N ;V=VG=>N 2V4?>2V44N =0 D0@<0:>B5@0?VN.
@>;>=3>20=0 D0@<0:>B5@0?VO (?>=04 24 B86=V) C ?0FVT=BV2 V7 =0207;82>-<0=V0:0;L=8<8
@>7;040<8 =5 282G0;0AL.

5@2>20 1C;V

;O 4>@>A;8E V ?0FVT=BV2 ;VB=L>3> 2V:C 4>70 AB0=>28BL 20 <3 =0 4>1C. @>;>=3>20=0 D0@
<0:>B5@0?VO (?>=04 3

030;L=V @5:><5=40FVW.

28G09=0 @5:><5=4>20=C 4>7C 20 <3 =0 4>1C <>6=0 7<5=H8B8 01> 71V;LH8B8. 0:A8<0;L=0 4>1>20
4>70 80 <3. >78 ?>=04 80 <3 =0 4>1C =5 282G0;8AL.

\$.C>:A5B8= <>65 1CB8 ?@87=0G5=89 1-2 @078 =0 4>1C ?V4 G0A W48 01> ?VA;O =5W.

VA;O ?@8?8=5==O ?@89>@30=V7 A;V4 2@0E>2C20B8 ?@8 ?@87=0G5==V V=H8E ?@5?0@0BV2 G8
?@8?8=5==V ;V:C20==O.

V4B@8 /: V I>4> V=H8E 0=B845?@5A0=BV2, 4;O 28O2;5==O ?>2=>3> 5D5:BC D;C>:A5B8=C <>65 1CB8
?>B@V1=> 3-4 B86=V.

>7C ?@5?0@0BC 4;O E2>@8E V7 =8@:>2>N 01> ?5GV=:>2>N =54>AB0B=VABN, 4;O E2>@8E
;VB=L>3> 2V:C V7 AC?CB=V<8 70E2>@N20==O<8, 0 B0:>6 4;O E2>@8E, O:V ?@89<0NBL V=HV
?@5?0@0B8, ?>B@V1=> 7=878B8.

0FVT=B8 ;VB=L>3> 2V:C. >7C ?V428ICNBL 7 >15@56=VABN. 0728G09 4>1>20 4>70 =5 ?5@528ICT 40
<3. 0:A8<0;L=0 4>1>20 4>70 AB0=>28BL 60 <3.

<5=H5=C 4>7C 01> V=B5@< ?@5?0@0BC (=0?@8;:04 :>6=C 4@C3C 4>1C) <>6=0 @5:><5=4C20B8
?0FVT=B0< 7 ?5GV=:>28<8 @>7;040<8 01> ?@8 AC?CB=V9 B5@0?VW ;V:0@AL:8<8 70A>10<8, O:V
?>B5=FBV9=> <>6CBL 270T<>4VOB8 V7 @>45?>

!;V4 C=8:0B8 @0?B>2>3> ?@8?8=5==O B5@0?VW D;C>:A5B8=>1EV4=> ?>ABC?>2> 7<5=HC20B8 4>7C ?@>BO3<< 1-2 B86=V2 7 <5B>N C=8:=5==O A8=4@> 7O2;ONBLAO A8<8 ?>3V@H5==O AB0=C ?V4 G0A 7=865==O 4>78 G8 ?@8?8=5==O ;V:C20==O ?@5?0@0B<, A;V4 ?>25@=CB8AO 4> ;V:C20==O ?>?5@54=L>N 5D5:B82=>N B5@0?52B8G=>N 4>7>N. '5@57 45O:89 G0A ;V:0@<>65 ?@>4>268B8 ?>ABC?>25 7=865==O 4>78.

VB8.

5 70AB>A>2CNBL 4VBO< G5@57 =54>AB0B=V9 ;;V=VG=89 4>A2V4 70AB>AC20==O ;V:0@AL:>3> 70A>1C @>45? C 4VB59.

5@54>7C20==O.

/8<8: =C4>B0, 1;N20==O, AC4<8, A5@F52>-AC48==V @>7;048 (2;;NG0NG8 ?>@CH5==O A8=CA>2>3> @8BG:>2V 0@8B 2:07CT =0 ?>4>265==O V=B5@20;C QT, A5@F52V =0?048, 2;;NG0NG8 @V4:V 28?04:8 Torsades de Pointes, @>7;048 48E0==O, 7W =5@2>2>W A8AB5<8 2V4 71C465==O 4> :<8, 3V?><0=VO. V:C20==O: ?@>2>:C20==O 1;N20==O 01> ?@><820==O H;C=:0, 70AB>AC20==O 0:B82>20=>3> 2C3V;;O, A>@15=BV2, A8<0B8G=0 V ?V4B@83> 0=B84>BC =5 VA=CT. \$>@A>20=89 4VC@57 01> 4V0;V7 <0;>5D5:B82=V ?@8 ?5@54>7C20==V @>45?C. 5:><5=4>20=> ?@>2>48B8 <=>VB>@8=3 A5@F52>W B0 48E0;L=>W 4VO;L=>ABV.

>1VG=V @50:FVW.

030;L=V ?>@CH5==O: A;01:VABL, 2;;NG0NG8 0AB5=VN, 2V4GCBBO B@57=>1, 2B><0, ?>30=5 A0 <>?>GCBBO, 2V4GCBBO E>;>4C, 60@C, 0=><0;L=V 2V4GCBBO, =5@>;5?B8G=89 A8=4@> I>:C :@>2V B0 ;VW A8AB5<8: B@><1>F8B>?5=VO, 35<>@03VG=V ?@>O28, ?V4H:V@=V 01> A;87>2V :@>2>28;828, B5=45=FVW 4> 28=8:=5==O A8=FV2. I>:C VW A8AB5<8: @50:FVW 3V?5@GCB;82>ABV, 2;;NG0NG8 0=3V>=52@>B8G=89 =01@O.; 0=0DV0:B8G=89 H>; 0=0DV;0:B>W4=V @50:FVW, A8@>20B:>20 E2>@>10 I>:C 5=4>:@8==>W A8AB5<8: =54>AB0B=O A5:@5FVO 0=B84VC@5B8G=>3> 3>@<=>C. 5B01>;VG=V ?>@CH5==O: 7=865==O 0?5B8BC, 2;;NG0NG8 0=>@5:AVN, 3V?>=0B@VT I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, @>7;048 C2038, 70?0<>@>G5==O, 48A3527VO, ;5B0@3VO, A>=;82VABL, 2;;NG0NG8 3V?5@A<=VN, A540FVN, B@5<>@, ?A8E><>B>@=0 3V?5@0:B82=VABL, 48A:V=57VO, 0B0:AVO, ?>@CH5==O :>@48=0FVW @CEV2, ;>=CA, AC4<8, 5?V;5?B8G=V =0?048, ?A8E><>B>@=5 71C465==O, ?>@CH5==O C2038, B@82>6=VABL, 48AD5@CH5==O :>=F5=B@0FVW, 0:0B87VO, 1C::>3;>A0;L=89 A8=4@<, A5@>B>=V=>289 A8=4@<, ?>@CH5==O ?0<OBV, 2;;NG0NG8 @0=:>25 ?@>1C465==O, 157A>==O ?@8 70A8?0==V, 157A>==O 2=>GV, 71C465==O, =5@2>7=VABL, 70=5?>:>T==O, =0?@C65=VABL, 7=865==O ;V1V4>, 2;;NG0NG8 2B@0BC ;V1V4>, ?>@CH5==O A=C, 2;;NG0NG8 ?0B>;>3VG=V A=>284V==O, =VG=V <0@5==O, 157A>==O, 45?5@A>=0;V70FVO, ?V428I5=89 =0AB@V9, 59D>@8G=89 =0AB@V9, ?>@CH5==O <8A;5==O, ?>@CH5==O >@307@307 3V?><0=VO, <0=VO, 30;NF8=0FVW, 068B0FVO, ?0=VG=V 0B0:8, ACWF840;L=V 4C254V=:0 (<>6CBL 1CB8 2=0A;V4>: >A=>2=>3> 70E2>@N20==O), A?;CB0=VABL A2V4<>ABV, @>7;048 <>28, 7. I>:C >@30=V2 7>@C: 70BC<0=5==O 7>@C, I>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC: HC< C 2CE0E. I>:C A5@F52>-AC48==>W A8AB5<8: 2V4GCBBO A5@F518BBO, H;C=>G:>2V 0@8B4>265==O V=B5@20;C QT, 2V4GCBBO ?@8;82V2, 2V4GCBBO 30@OG8E ?@8;82V2, 3V?>B5=7VO, 20A:C;VB, 207>48;OB0FVO. I>:C 48E0;L=>W A8AB5<8: ?>7VE0==O, 7048H:0, D0@8=3VB, 48E0;L=V @>7;048 (70?0;L=V ?@>F5A8 G8 @V7=><0=VB=V 3VAB>?0B>;>3VG=V 7DV1@>7, =>A>20 :@>2>B5G0. I>:C B@02=>3> B@0:BC: 4V0@50, =C4>B0, 1;N20==O, 48A?5?AVO, ACEVABL 2 @>BV, 48AD03VO, 1V;L 2 AB@02>E>4V, H;C=:>2>-.8H:>20 :@>2>B5G0, 2;;NG0NG8 =09G0ABVH5 :@>2>B5GC 7 OA5=, 1;N20==O :@>2N, :@>2O=8ABV 28?>@>6=5==O, @5:B0;L=V :@>2>B5GV, 35<>@03VG=C 4V0@5N, <5;5=C, V H;C=:>2C :@>2>B5GC 7 28@07:8. I>:C 35?0B>1V;V0@=>W A8AB5<8: V4V>A8=:@0B8G=89 35?0B8B. I>:C H:V@8 B0 ?V4H:V@=>W ;;VB:>28=8: 28A8?0==O, 2;;NG0NG8 5@8B5;V0B82=V 28A8?0==O, ?VB=8FO, 5@8B5<0B>7=V, D>;V:C;O@=V, 35=5@0;V7>20=V;<0:C;O@=V, <0:C;>?0?C;O@=V, ?0?C;O@=V, :V@>?>4V1=V 28A8?0==O, A25@1;OGV 28A8?0==O, 2578:C;O@=V 28A8?0==O, 28A8?0==O =02:>;> ?C?:0, @50:FVW D>B>GCB;82>ABV, @<=0 5@8B5<0, I> <>65 ?@>3@5AC20B8 4>

A8=4@>=A>=0 01> B>:A8G=>3> 5?V45@<0;L=>3> =5:@>;V7C (A8=4@< 09T;;0), A25@1V6,
:@>?82O=0, ?C@?C@0, 0;>?5FVO, 5:EV<>78.
I>:C :VAB:>2>-<O7>2>W A8AB5<8: 0@B@0;3VO, ?>AV?C20==O< O7V2,
I>:C A5G>284V;L=>W A8AB5<8: G0AB5 A5G>28?CA:0==O, 487C@VO, 70B@87;048 A5G>28?CA:0==O,
?>;V0:C@VO.
I>:C @5?@>4C:B82=>W A8AB5<8: 3V=5:>;>3VG=0 :@>2>B5G0, 2;;NG0NG8 :@>2>B5GV 7 H89:8
<0B:8, 48ADC=:FVN <0B:8, <0B:>2C :@>2>B5GC, :@>2>B5GC 7 35=VB0;VW2, <5=><5B@>@03VN,
?>;V<5B@>@03VN, ?>AB<5=>?0C70;L=C :@>2>B5GC, 203V=0;L=C :@>2>B5GC; 5@5:B8;L=0
48ADC=:FVO, @>7;048 5O:C;OFVW, 2;;NG0NG8 =54>AB0B=VABL 5O:C;OFVW, 48ADC=:FVN
5O:C;OFVW, ?5@54G0A=C 5O:C;OFVN, 70B@8;OFVW, @5B@>3@04=C 5O:C;OFVN, A5:AC0;L=0
48ADC=:FVO, 30;0:B>@50, 3V?5@?@>;0:B8=5
>A;V465==O: 7=865==O <0A8 BV;0, ?>@CH5==O ?>:07=8:V2 DC=:FVW ?5GV=:8.
V4 G0A ?@89>:A5B8=C G8 2V4@07C ?VA;O ?@8?8=5==O 70AB>AC20==O D;C>:A5B8=C ?>2V4>
<;O;>AL ?@> 28?04:8 ACWF840;L=8E 4C<>: B0 ?>254V=:8. (482. @>74V; «A>1;82>ABV
70AB>AC20==O»).

5@5;><8 :VAB>.: 5?V45;>3VG=V 4>A;V465==O, ?@>2545=V 2 >A=>2=>:V2 V AB0@H5, ?>:07CNBL
?V428I5==O @878:C ?5@5;>: C ?0FVT=BV2, O:V >B@8@8 72>@>B=>3> 70E?>;5==O A5@>B>=V=C B0
0=B845?@5A0=BV2. 5E0=V7< @>728B:C 40=8E @878:V2 =52V4><89.
!8<8 2V4. @8?8=5==O ?@89>:A5B8=C ?5@5206=> ?@872>48BL 4> A8
09G0ABVH8<8 A8<0<8 A83> G8 A5@54=L>3> ABC?5=O BO6:>ABV, 0;5<>6CBL 1CB8 V BO6:>3>
ABC?5=O BO6:>ABV V B@820;8<8 (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O»). 28G09=>
28=8:0NBL ?@>BO3<< ?5@H8E 4=V2 ?VA;O ?@8?8=5==O 70AB>AC20==O D;C>:A5B8=C. "0:8< G8=><,
@5:><5=4>20=> ?>ABC?>2> 7=86C20B8 4>7C D;C>:A5B8=C ?@>BO3<< I>=09<5=H5 1-2 B86=V2
2V4?>2V4=> 4> ?>B@51 ?0FVT=B0. (482 @>74V;8 «!>AV1 70AB>AC20==O B0 4>78» B0 «A>1;82>ABV
70AB>AC20==O»).

"5@ABV.4 @>:8.

#<>28 715@V30==O.

15@V30B8 ?@8 B50! 2 >@83V=0;L=V9 C?0:>2FV.

15@V30B8 2 =54>ABC?=>

#?0:>2:0.

> 10 :0?AC; C AB@8?V, ?> 6 AB@8?V2 C :0@B>==V9 C?0:>2FV.

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

8@>1=8:.

!0= \$0@<0ALNB8:0; =40AB@V7 B4.

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

!C@259 214, 025@=<5=B =40AB@V0; @VO, \$070 , !V;L20AA0 396230 (#." 04@0 & 030@ %025;V),
=4VO.