

!"#&/

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

®

(VESICARE®)

!,:04:

4VNG0 @5G>28=0: solifenacin succinate;

1 B01;5B:0 ;VD5=0F8=C AC:F8=0B 5 <3 01> 10 <3;

4>?>28=8: ;0:B>78 <=>3V4@0B, :@>E<0;L :C:C@C47O=89, 3V?@><5;>70, <03=VN AB50@0B;

A:;04 >1>;>=:8 4;O B01;5B>: 5 <3: >?04@V 6>2B89 03F12967 (3V?@><5;>70, B0;L:, <0:@>3>; 8000, B8B0=C 4V>:A84 (171), 70;V70 >:A84 6>2B89 (172));

4;O B01;5B>: 10 <3: >?04@V @>65289 03F14895 (3V?@><5;>70, B0;L:, <0:@>3>; 8000, B8B0=C 4V>:A84 (171), 70;V70 >:A84 G5@2>=89 (172)).

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 :@C3;>W D>@<8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 1;V4>-6>2B>3> :>;L>@C 7 ;>3>B8?<< B0 ?>7=0G:>N «150» 7 >4=>3> 1>;C;

B01;5B:8 10 <3 :@C3;>W D>@<8, 2:@8BV ?;V2:>2>N >1>;>=:>N 1;V4>-@>652>3> :>;L>@C 7 ;>3>B8?<< B0 ?>7=0G:>N «151» 7 >4=>3> 1>;C.

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, I> 70AB>A>2CNBLAO 2 C@>;>3VW. 0A>18 4;O ;V:C20==O G0AB>3> A5G>28?CA:0==O B0 =5B@8<0==O A5GV. >4 "%G04B D08.

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

\$0@<0:>48=0

!>;VD5=0F8= T :>=:C@5=B=8<, A?5F8DVG=8< 0=B03>=VAB< E>;V=5@3V=>28E @5F5?B>@V2. !5G>289 F5B8;E>;V= A:>@>GCT 3;04:V<078 45B@C7>@0,

2?;820NG8 =0 2V @5F5?B>@8, I> ?5@5206=> ?@54AB02;5=V 3 ?V4B8?>

# 4>A;V465==OE in vitro B0 in vivo 1C;> 2AB0=>2;5=>, I> A>;VD5=0F8= T :>=:C@5=B=8< A?5F8DVG=8< 0=B03>=VAB< E>;V=5@3VG=8E

@5F5?B>@V2 ?5@5206=> 3 ?V4B8?C. "0:>6 1C;> 2AB0=>2;5=>, I> A>;VD5=0F8= <0T A;01:C A?>@V4=5=VABL 01> 2V4ACB=VABL A?>@V4=5=>ABV 7 V=H8<8 @5F5?B>@<8 V B5AB>20=8<8 V>==8<8 :0=0;0<8.

D5:B82=VABL ?@5?0@0BC, O:C 282G0;8 C :V;L:>E ?>42V9=8E A;V?8E @0=4>20=8E :>=B@>;L>20=8E ;:V=VG=8E 4>A;V465==OE C G>;>2V:V2 B0

6V=>: V7 A8=4@><< 3V?5@0:B82=>3> A5G>2>3> AB5@V30;0AO 265 =0 1-B03<< =0ABC?>8E 12 B86=V2 ;V:C20==O. # 2V4:@8B8E 4>A;V465==OE

?@8 B@820;>AC20==V ?>:070=>, I> 5D5:B82=VABL ?V4B@8BO3<< I>=09<5=H5 12 \$0@<0:>:V=5B8:0.

IA>@IFVO. VA;O ?@89>. <0:A8<0;L=0 :>=F5=B@0FVO A>;VD5=0F8=C C ?;072V (C<sub>m0x</sub>) 4>AO30TBLAO G5@57 3-8 3>48=. =0G5==O G0AC

4>AO3=5==O <0:A8<0;L=>W :>=F5=B@0FVW (t<sub>max</sub>)=5 70;568BL 2V4 4>78 ?@5?0@0BC. =0G5==O C<sub>m0x</sub> V ?;>IV ?V4 :@82>N (AUC) 71V;LHCNBLAO

?@>?>@FV9=> 4> 4>78 C ?@>C<sub>m0x</sub> B0 AUC A>;VD5=0F8=C =5 2?;820T.

>7?>4V;. !>;VD5=0F8= 7=0G=>N N (<0965 98 %) 72'O7CTBLAO 7 1V;:0<8 ?;07<8 :@>2V, 3>;>2=8< G8=>< 7 □1-:8A;8< 3;V:>?@>B5W=>

5B01>;V7!>;VD5=0F8= 7=0G=>N N <5B01>;V7CTBLAO C ?5GV=FV, 3>;>2=8< G8=>< F8B>E@><< 450 34 (CYP3A4). !8AB5<=89 :;V@5=A  
A>;VD5=0F8=C AB0=>28BL ?@81;87=> 9,5 ;/3>48=8, V B5@4 9>3> =0?V2282545==O AB0=>28BL 45-68 3>48=. VA;O ?5@>@0;L=> ?@89>2V, :@V<  
A>;VD5=0F8=C, 1C2 V45=B8DV:>20=89 1 D0@<0:>;>3VG=> 0:B82=89 (4R-3V4@>:A8A>;VD5=0F8=) V 3 =50:B82=V <5B01>;VB8 (N-3;N:C@>=V4,  
N->:A84 V 4R-3V4@>:A8-N->:A84 A>;VD5=0F8=C).

:A:@5FVO. VA;O >4=>@07>2>3> 70AB>AC20==O 10<3 [14C-3>]-A>;VD5=0F8=C ?@81;87=> 70 % @04V>0:B82=>W O2;OTBLAO C A5GV V 23 % C  
D5:0;VOE. # A5GV ?@81;87=> 11 % @04V>0:B82=>W 48BLAO C 283;O4V =57W 0:B82=>W AC1AB0=FVW; ?@81;87=> 18 % C 283;O4V <5B01>;VBC N-  
>:A84C, 9 % C 283;O4V <5B01>;VBC 4R-3V4@>:A8-N->:A84 V 8 % C 283;O4V 4R-3V4@>:A8<5B01>;VBC (0:B82=89 <5B01>;VB).

>7>20 70;56=VABL. # ?@>7 D0@<0:>:V=5B8:0 ?@5?0@0BC T ;V=V9=>N.

A>I;82>ABV D0@<0:>:V=5B8:8 2 >:@5<8E :0B53>@VOE ?0FVT=BV2.

V.: 5<0T =5>1EV4=>ABV :>@83C20B8 4>7C 70;56=> 2V4 2V:C E2>@8E. >A;V465==O ?>:070;8, I> 5:A?>78FVO A>;VD5=0F8=C ( 5 V 10<3), 28@065=0  
C 283;O4V AUC, 1C;0 ?>4V1=>N C 74>@>28E ;N459 ;VB=L>3> 2V:C (2V4 65 4> 80 @>:V2) V C 74>@>28E ;N459<>;>4>3> B0 7@V;>3> 2V:C (<  
55 @>:V2). !5@54=O H284:VABL 01A>@1FVW, 28@065=0 C 283;O4V  $t_{max}$ , 1C;0 45I> =86G>N, 0 :V=F5289 ?5@V>4 =0?V2282545==O ?@81;87=> =0 20  
% B@820;VH89 C ?0FVT=BV2 ;VB=L>3> 2V:C. &V =57=0G=V 2V4ABV =5 T ;;V=VG=> 7=0GCI8<8.

\$0@<0:>:V=5B8:C A>;VD5=0F8=C =5 282G0;8 C 4VB59 B0 ?V4;VB:V2.

!B0BL. \$0@<0:>:V=5B8:0 A>;VD5=0F8=C =5 70;568BL 2V4 AB0BV ?0FVT=B0.

0A0. 0A>20 ?@8=0;56=VABL =5 2?;820T =0 D0@<0:>:V=5B8:C A>;VD5=0F8=C.

8@:>20 =54>AB0B=VABL. AUC B0  $C_{m0x}$  A>;VD5=0F8=C C ?0FVT=BV2 V7 ;53:>N B0 ?>N =8@:>2>N =54>AB0B=VABN =57=0G=> 2V4@V7=ONBLAO  
2V4 2V4?>2V4=8E ?>:07=8:V2 C 74>@>28E 4>1@>2>;LFV2. # ?0FVT=BV2 V7 BO6:>N =8@:>2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C<= 30 <; 70  
E28;8=C) 5:A?>78FVO A>;VD5=0F8=C 7=0G=> 28I0 71V;LH5==O  $C_{m0x}$  AB0=>28BL ?@81;87=> 30 %, AUC ?>=04 100 % B0 ?5@V>4  
=0?V2282545==O ?>=04 60 %. V47=0G5=89 AB0B8AB8G=> 7=0GCI89 270T<>72`O7>: <:@50B8=V=C V ;;V@5=A< A>;VD5=0F8=C. \$0@<0:>:V=5B8:C  
C ?0FVT=BV2, O:V ?@>E>48;8 35<>4V0;V7, =5 282G0;8.

5GV=:>20 =54>AB0B=VABL. # ?0FVT=BV2 V7 ?>N ?5GV=:>2>N =54>AB0B=VABN (?>:07=8: '09;4-N 2V4 7 4> 9) 7=0G5==O  $C_{m0x}$  =5 7AB0T =0 60 % B0  
?5@V>4 =0?V2282545==O 71V;LHCTBLAO 242VGV. \$0@<0:>:V=5B8:C C ?0FVT=BV2 V7 BO6:>N =8@:>2>N =54>AB0B=VABN =5 282G0;8.

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

>:070==O.

!8<0B8G=5 ;V:C20==O C@35=B=>3> (V3>) =5B@8<0==O A5GV B0/01> G0AB>3> A5G>28?CA:0==O, 0 B0:>6 C@35=B=8E (V782V2 4>  
A5G>28?CA:0==O, E0@0:B5@=8E 4;O ?0FVT=BV2 V7 A8=4@>>> 3V?5@0:B82=>3> A5G>2>3>

@>B8?>:070==O.

@5?0@0B ?@>B8?>:070=89 ?0FVT=B0< V7 ?V428I5=>N GCB;82VABN 4> 0:B82=>W AC1AB0=FVW 01> 4>1C4L-O:>W 7 4>?>28=; ?0FVT=B0< V7  
70B@8N A5G>28?CA:0==O, V7 BO6:8<8 H;C=:>2>.:8H:>28<8 70E2>@N20==O<8 (2;:NG0NG8 B>:A8G=89 <530:>;>=), V7 3@02VA G8 V7  
70:@8B>:CB>2>N 3;0C:><>N B0 ?0FVT=B0< V7 @878:> @>728B:C F8E AB0=V2; ?@8 ?@>2545==V 35<>4V0;V7C (482. @>74V; «\$0@<0:>:V=5B8:0»);  
V7 BO6:>N ?5GV=:>2>N =54>AB0B=VABN (482. @>74V; «\$0@<0:>:V=5B8:0»); ?0FVT=B0< V7 BO6:>N =8@:>2>N =54>AB0B=VABN 01> ?5GV=:>2>N  
=54>AB0B=VABN A5@54=L>3> ABC?5=O BO6:>ABV, O:V ?5@51C20NBL =0 ;V:C20==V A8;L=88 V=3V1VB>@0<8 F8B>E@>CYP3A4, =0?@8::04,  
:5B>:=>07>;> (482. @>74V; «70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

\$0@<0:>;>3VG=V 270T<>4VW.

4=>G0A=89 ?@89>< V=H8E ;V:0@AL:8E ?@5?0@0BV2 7 0=B8E>;V=5@3VG=8<8 2;0AB82>ABO<8 <>65 <0B8 28@07=VHV B5@0?52B8G=V, 0 B0:>6 =51060=V 5D5:B8. VA;O ?@8?8=5==O 70AB>AC20==O 578:0@C® 4> ?@89>1V2 0=B8E>;V=5@3VG=>W B5@0?VW =5>1EV4=> 28B@8<0B8 ?@81;87=> >4=>B86=5289 V=B5@20;. "5@0?52B8G=89 5D5:B A>;VD5=0F8=C <>65 7<5=H8B8AO ?@8 AC?CB=L>AC20==V 03>=VABV2 E>;V=5@3VG=8E @5F5?B>@V2. !>;VD5=0F8= <>65 7=86C20B8 5D5:B ;V:0@AL:8E ?@5?0@0BV2, O:V AB82>-.8H:>2>3> B@0:BC, B0:8E O: <5B>;>?@0

\$0@<0:>:V=5B8G=V 270T<>4VW.

>A;V465==O in vitro?>:070;>, I> A>;VD5=0F8= C B5@0?52B8G=8E :=F5=B@0FVOE =5 ?@83=VGCT A><8 ?5GV=:8 CYP1A1/2, 2C9, 2C19, 2D6, G8 3A 4. "0:8< G8=><, <0:>9<>2V@=>, I> A>;VD5=0F8= 2?;820T =0 ;;V@5=A ;V:0@AL:8E 70A>1V2, I><5B01>;V7CNBLAO D5@<5=B0<8 CYP.

?;82 V=H8E ;V:0@AL:8E 70A>1V2 =0 D0@<0:>:V=5B8:C A>;VD5=0F8=C.

!>;VD5=0F8= <5B01>;V7CTBLAO D5@<5=B>< CYP3A4. 4=>G0A=5 70AB>AC20==O :5B>:=07>;C (200 <3/4>1C), A8;L=>3> V=3V1VB>@0 CYP3A4 ?@872>48;> 4> 42>:@0B=>3> ?V428I5==O AUC A>;VD5=0F8=C, 2 B>9 G0A O: ?@89> :5B>:=07>;C 2 4>7V 400 <3/4>1C A?@8G8=OT ?V428I5==O AUC A>;VD5=0F8=C 2 3 @078. "0:8< G8=><, <0:A8<0;L=C 4>7C 578:0@C® =5>1EV4=> >1<568B8 4> 5 <3 ?@8 >4=>G0A=>AC20==V 7 :5B>:=07>;<< G8 B5@0?52B8G=8E 4>7 V=H8E 0:B82=8E V=3V1VB>@V2 D5@<5=BC CYP3A4 (=0?@8::04, @8B>=02V@C, =5;V=02V@C, VB@0:=>07>;C) (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»).

4=>G0A=5 70AB>AC20==O A>;VD5=0F8=C B0 A8;L=>3> V=3V1VB>@0 D5@<5=BC CYP3A4 ?@>B8?>:070=5 ?0FVT=B0< V7 BO6:>N =8@:>2>N 01> ?> 28@065=>N ?5GV=:>2>N =54>AB0B=VABN.

5 4>A;V46C20;8 2?;82 D5@<5=BV2 V=4C:FVW =0 D0@<0:>:V=5B8:C A>;VD5=0F8=C V 9>3> <5B01>;VBV2, 0 B0:>6 4VN AC1AB@0BV2 7 ?V428I5=>N A?>@V4=5=VABNCYP3A4 B0 9>3> <5B01>;VBV2 =0 5:A?>78FVN A>;VD5=0F8=C. A:V;L:8 A>;VD5=0F8=<5B01>;V7CTBLAO D5@<5=B>< CYP3A4, D0@<0:>:V=5B8G=V 270T<>4VW <>6;82V 7 V=H8<8 AC1AB@0B0<8 FL>3> D5@<5=BC, I> <0NBL ?V428I5=C A?>@V4=5=VABL (=0?@8::04, 25@0?0 <, 48;BV075<><), B0 V=4C:B>@0<8 D5@<5=BC CYP3A4 (=0?@8::04, @8D0<, D5=VB>W=><, :0@10<075?V=><).

?;82 A>;VD5=0F8=C =0 D0@<0:>:V=5B8:C ;V:0@AL:8E 70A>1V2.

5@>@0;L=V :=B@0F5?B828.

@89>< ?@5?0@0BC 578:0@® =5 2?;820T =0 D0@<0:>:V=5B8G=C 270T<>4VN A>;VD5=0F8=C 7 :<1V=>20=8<8 ?5@>@0;L=8<8 :=B@0F5?B820<8 (5B8=V;5AB@04V>;;/52>=>@35AB@5;).

0@D0@8=.

@89>< ?@5?0@0BC 578:0@® =5 2?;820T =0 D0@<0:>:V=5B8G=C 270T<>4VN R-20@D0@8=C G8 S- 20@D0@8=C 01> 9>3> 2?;82 =0 ?@>B@< <1V=>289 G0A.

83>:A8=.

@89>< ?@5?0@0BC 578:0@® =5 2?;820T =0 D0@<0:>:V=5B8:C 483>:A8=C.

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

5@54 ?>G0B:>< ;V:C20==O ?@5?0@0B< =5>1EV4=> 2AB0=>28B8 V<>2V@=VABL V=H8E ?@8G8= G0AB>3> A5G>28?CA:0==O (A5@F520 =54>AB0B=VABL 01> 70E2>@N20==O =8@>:). /:I> 28O2;5=0 V=D5:FVO A5G>282V4=8E H;OEV2, A;V4 @>?>G0B8 2V4?>2V4=C 0=B810:B5@V0;L=C B5@0?VN.

@5?0@0B =5>1EV4=> ?@89<0B8 7 >15@56=VABN ?0FVT=B0

V7 ;;V=VG=> 7=0GCI>N >1AB@C:FVTN 28EV4=>3> >B2>@C A5G>2>3> ?@872>48BL 4> @878:C 70B@828?CA:0==O;

7V H;C=:>2>-.8H:>28<8 >1AB@C:B82=8<8 70E2>@N20==O<8;

V7 @878:>< 7=865==O <>B>@8:8 H;C=:>2>-.8H:>2>3> B@0:BC;

V7 BO6:>N =8@:>2>N (:;V@5=A :@50B8=V=C ≤ 30 <; 70 E28;8=C) B0 ?>N ?5GV=:>2>N (?>:07=8: '09;4-□N 2V4 7 4> 9) =54>AB0B=VABN (482.  
@>74V;8 «!>AV1 70AB>AC20==O B0 4>78» B0 «\$0@<0.:V=5B8:0»); 4>78 4;O F8E ?0FVT=BV2 =5 <ONBL ?5@528IC20B8 5 <3;  
?@8 >4=>G0A=> A8;L=8E V=3V1VB>@V2 CYP3A4, =0?@8;:04, :5B>:=>07>;C (482. @>74V;8 «!>AV1 70AB>AC20==O B0 4>78» B0 «70T<>4V0  
7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»);  
V7 3@865N AB@02>EV4=>3> >B2>@C 4V0D@03<8 B0/01> H;C=:>2>-AB@02>EV4=8< @5D;N:A<< B0/01> B8<, EB> >4=>G0A=> ?@89<0T  
;V:0@AL:V ?@5?0@0B8 (B0:V O: 1VAD>AD>=0B8), O:V<>6CBL A?@8G8=8B8 01> ?>A8;8B8 57>D03VB;  
2535B0B82=>N =59@>?0BVTN.

# ?0FVT=BV2 7 D0:B>@0<8 @878:C, B0:8<8 O: @0=VH5 70@5TAB@>20=89 A8=4@< ?>4>265==O V=B5@20;C QT, B0 3V?>:0;VTAB5@V30;>AO  
?>4>265==O V=B5@20;C QT V B@V?>BV==O<5@5EBV==O (*torsade de pointes*).

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC =5 4>A;V465=0 4;O E2>@8E V7 ?V428I5=>N 0:B82=VABN ADV=:B5@0 =59@>35==>3>  
?>E>465==O.

0FVT=B0< V7 @V4:VA=8<8 A?04:>28<8 D>@<0<8 =5?5@5=>A8<>ABV 30;0:B>78, Lapp-45DVF8B<< ;0:B078 01> 7 ?>@CH5==O< 3;N:>7>-30;0:B>7=>W  
<0;L01A>@1FVW =5 A;V4 ?@89<0B8 ?@5?0@0B.

# 45O:8E ?0FVT=BV2, O:V 70AB>A>2C20;8 A>;VD5=0F8=C AC:F8=0B, ?>2V4<;O;>AO ?@> 0=3V>=52@>B8G=89 =01@O: 7 >1AB@C:FVTN  
48E0;L=8E H;OEV2. @8 28=8:=5==V =01@O:C 2V=:5 ;V:C20==O A>;VD5=0F8=< AC:F8=0B< A;V4 ?@8?8=8B8 B0 268B8 2V4?>2V4=8E 70E>4V2 01>  
?@87=0G8B8 =0;56=5 ;V:C20==O.

# 45O:8E ?0FVT=BV2, O:V 70AB>A>2C20;8 A>;VD5=0F8=C AC:F8=0B, A?>AB5@V30;8AO 0=0DV;0:B8G=V @50:FVW. @8 28=8:=5==V  
0=0DV;0:B8G=8E @50:FV9 ;V:C20==O A>;VD5=0F8=< AC:F8=0B< A;V4 ?@8?8=8B8 B0 268B8 2V4?>2V4=8E 70E>4V2 01> ?@87=0G8B8 =0;56=5  
;V:C20==O.

0:A8<0;L=89 5D5:B ?@5?0@0BC 4>AO30TBLAO =5 @0=VH5, =V6 G5@57 4 B86=V.

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

03VB=VABL.

5<0T ;;V=VG=8E 40=8E ?@> 6V=>;, O:V 70203VB=V;8 ?V4 G0A 70AB>AC20==O A>;VD5=0F8=C. >A;V48 =0 B20@8=0E =5 28O28;8 ?@O<>W  
=5A?@8OB;82>W 4VW =0 D5@B8;L=VABL, @>728B>: 5<1@V>=0/?;>40 01> ?>;>38. >B5=FV9=89 @878: =52V4<<89. !;V4 4>B@815@56=>ABV ?@8  
70AB>AC20==V 40=>3> ?@5?0@0BC 203VB=8< 6V=:0  
>4C20==O 3@C44N.

5<0T 40=8E I>4> 5:A:@5FVW A>;VD5=0F8=C C 3@C4=5 <>;>. # <8H59 A>;VD5=0F8= B0/01> 9>3> <5B01>;VB8 ?@>=8:0NBL C <>;>:> V  
A?@8G8=ONBL 4>7>70;56=C =54>AB0B=VABL @>ABC C =>2>=0@>465=8E<8H59. 0AB>AC20==O 578:0@C® =5 @5:><5=4CTBLAO 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.**

# 72'O7:C 7 B8<, I> A>;VD5=0F8=, O: V V=HV 0=B8E>;V=5@3VG=V ?@5?0@0B8, <>65 A?@8G8=8B8 =5GVB:VABL 7>@C, V =5G0AB> A>=;82VABL  
B0 ?V428I5=C 2B<<;N20=VABL (482. @>74V; «>1VG=V 5D5:B8»), ?@89< ?@5?0@0BC <>65 =530B82=> 2?;820B8 =0 740B=VABL :5@C20B8 02B>  
<>1V;5< B0 V=H8<8 <5E0=V7<0<8.

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

>@>A;V, 2.;NG0NG8 >AV1 ;VB=L>3> 2V:C:@5:><5=4>20=0 4>70 5 <3 ?@5?0@0BC 1 @07 =0 4>1C. /:I> =5>1EV4=>, 4>7C <>6=0 ?V428I8B8 4> 10 <3 1 @07 =0 4>1C.

0FVT=B8 7 =8@:>2>N =54>AB0B=VABN: =5 ?>B@V1=0 :>@5:FVO 4>78 4;O ?0FVT=BV2 7 ?>N B0 A5@54=L>3> ABC?5=O BO6:>ABV =8@:>2>W =54>AB0B=>ABV (:;V@5=A :@50B8=V=C > 30 <:/E2). 0FVT=B0< 7 BO6:8< ABC?5=5< =8@:>2>W =54>AB0B=>ABV (:;V@5=A :@50B8=V=C <= 30 <:/E2) A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?@5?0@0B V 70AB>A>2C20B8 =5 1V;LH5 =V6 5<3 1 @07 =0 4>1C (482. @>74V; «\$0@<0>:V=5B8:0»). 0FVT=B8 7 ?5GV=:>2>N =54>AB0B=VABN: =5 ?>B@V1=0 :>@5:FVO 4>78 4;O ?0FVT=BV2 7 ?>N ?5GV=:>2>N =54>AB0B=VABN. 0FVT=B0< 7 ?>N ?5GV=:>2>N =54>AB0B=VABN (?>.07=8: '09;4-N 7-9) A;V4 ?@89<0B8 ?@5?0@0B 7 >15@56=VABN V =5 ?5@528IC20B8 4>7C20==O 5<3 1 @07 =0 4>1C (482. @>74V; «\$0@<0>:V=5B8:0»).

@8 70AB>AC20==V ?>BC6=8E V=3V1VB>@V2 F8B>E@><0:A8<0;L=0 4>70 ?@5?0@0BC 578:0@® <0T 1CB8 >1<565=0 5 <3 ?@8 >4=>G0A=>:>=07>;> <01> B5@0?52B8G=8<8 4>70<8 V=H8E A8;L=8E V=3V1VB>@V2 V7>D>@<8 F8B>E@>=02V@C, =5;DV=02V@C, VB@0:>=07>;C (482. @>74V; «70T <>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

578:0@® ?@89<0B8 ?5@>@0;L=>, :>2B0B8 FV;V B01;5B:8, 70?820NG8 @V48=>N, =570;56=> 2V4 ?@89>

**VB8.**

5 4>A;V46C20;8 157?5:C B0 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC 4VBO<, B>® =5 A;V4 ?@87=0G0B8 FV9 :0B53>@VW ?0FVT=BV2.

**5@54>7C20==O.**

/8<8.  
5@54>7C20==O A>;VD5=0F8=C AC:F8=0BC <>65 ?@8725AB8 4> BO6:8E 0=B8E>;V=5@3VG=8E 5D5:BV2. 0928I0 4>70 A>;VD5=0F8=C AC:F8=0BC, ?@89=OB0 28?04:>2> >4=8< ?0FVT=B><, AB0=>28;0 280 <3 ?@>BO3>< 5 3>48=, A?>AB5@V30;8AO 73> AB0=C, I> =5 ?>B@51C20;8 3>A?VB0;V70FVW.

V:C20==O. # 28?04:C ?5@54>7C20==O A>;VD5=0F8=C AC:F8=0BC ?0FVT=B>2V =5>1EV4=> ?@89=OB8 0:B82>20=5 2C3V;;O. >65 1CB8 :>@8A=8< ?@><820==O H;C=:0, O:I> 2>=> 7@>1;5=5 ?@>BO3>< 1 3>48=8, 0;5 =5 A;V4 28;;8:0B8 1;N20==O.  
)>4> V=H8E 0=B8E>;V=5@3VG=8E 5D5:BV2, B> A8<8 A;V4 ;V:C20B8 B0:8< G8=>

BO6:V 0=B8E>;V=5@3VG=V 5D5:B8 7 1>:C F5=B@0;L=>W =5@2>2>W A8AB5<8, B0:V O: 30;NF8=0FVW 01> ?V428I5=0 71C4;82VABL: ;V:C20==O DV7>AB83< 01> :0@10E>;<;

AC4><8 01> ?V428I5=C 71C4;82VABL: ;V:C20==O 15=7>4V075?V=0<8; =54>AB0B=VABL 7 1>:C >@30=V2 48E0==O: ;V:C20==O HBCG=0 25=B8;OFVO ;535=V2;

B0EV:0@4VO: ;V:C20==O 15B0-1;>:0B>@0<8; 70B@828?CA:0==O: ;V:C20==O :0B5B5@870FVO;

G=8<8 :@0?;O<8, =0?@8:;04 ?V;>:0@?V=<, B0/01> @>7 /: V C 28?04:0E ?5@54>7C20==O V=H8<8 0=B8E>;V=5@3VG=8<8 70A>10<8, >A>1;82C C203C A;V4 ?@84V;OB8 ?0FVT=B0< 7V 2AB0=>2;5=8< @878:> < ?>4>265==O V=B5@20;C QT (?@8 3V?>:0;VT4=>G0A=>AC20==V ?@5?0@0BV2, I> A?@8G8=ONBL ?>4>265==O V=B5@20;CQT) V ?0FVT=B0< 7V 70E2>@N20==O<8 A5@FO (VH5:0@40, 0@8BAB0B=VABL).

**>1VG=V@50:FVW.**

578:0@® <>65 A?@8G8=8B8 ?>1VG=V 5D5:B8, ?>2O70=V 7 0=B8E>;V=5@3VG=>N 4VTN A>;VD5=0F8=C, O:V, O: ?@028;>, A;01:V 01> ?> G0AB>B0 70;568BL 2V4 4>78 ?@5?0@0BC.

09G0ABVH5 ?>1VG=5 O28I5 ACEVABL C @>BV, I> A?>AB5@V30;0AO C 11 % ?0FVT=BV2, O:V >B@8C 5 <3 =0 4>1C, C 22 % ?0FVT=BV2, O:V >B@8 . 8@065=VABL ACE>ABV C @>BV, O: ?@028;>, 1C;0 A;01:>N, V BV;L:8 C ?>>48=>:8E 28?04:0E ?@872>48;0 4> ?@8?8=5==O ;V:C20==O. 030;⊗ ;V:0@AL:89 ?@5?0@0B 4>A8BL 4>1@5 ?5@5=>A82AO (1;87L:> 99 %), V ?@81;87=> 90 % ?0FVT=BV2 ?@89<0;8 ?@5?0@0B ?@>BO3<< ?>2=>3> ?5@V>4C 4>A;V465==O, O:89 B@8202 12 B86=V2.  
 # B01;8FV =86G5 =02545=V V=HV ?>1VG=V 5D5:B8, 70@5TAB@>20=V ?@8 ?@>2545==V ;;V=VG=8E 4>A;V465=L 578:0@C® B0 ?VA;O@5TAB@0FV9=>4V.

;0A8DV:0FVO MedDRA	C65 G0AB> >1/10	'0AB> > 1/100, <1/10	5G0AB> > 1/1000, <1/100	V4:VA=V > 1/10000, <1/1000	C65 @V4:VA=V <1/10000	52V4><> (@>?>2AN4- 65=VABL =5 <>6=0 >FV=8B8 =0 >A=>2V =0O2=8E 40=8E)
=D5:FVW B0 V=207VW			=D5:FVW A5G>282V4=8E H;OEV2, F8AB8B			
1>:C VW A8AB5 <8						=0DV;0:B8G=0 @50:FVO*
1>:C <5B01>;V7						=865==O 0?5B8BC*, 3V?5@:0;VT
A8EVG=V @>7;048					0;NF8=0- FVW*, A?;CB0=VABL A2V4> <>ABV*	0@5==O*
>@CH5==O 7 1>:C =5@2>2>W A8AB5<8			!>=:82VABL, ?>@CH5==O A <0:C	0?0<>@>- G5==O*, 3>;>2=89 1V;L*		
1>:C >@30=V2 7>@C		5GVB:VABL 7>@C	!CEVABL >G59			;0C:><0*

1>:C A5@FO						Torsades de pointes* >4>265==O V=B5@20;C QT =0 5;5:B@>:0@- 4V>3@0 \$V1@8;OFVO ?5@54A5@4L* V4GCBBO A5@F518BBO* "0EV:0@4VO* 8AD>=VO*
1>:C >@30=V2 48E0==O, 3@C4=>W ;;VB:8 B0 A5@54>ABV==O			!CEVABL A;87>2>W >1>;>=:8 =>A>2>W ?>@>6=8=8			
1>:C H;C=:>2>- :8H:>2>3> B@0:BC	!CEVABL C @>BV	0?>@, =C4>B0, 48A?5?AVO, 1V;L C 682>BV	0AB@>- 57>D0350;L- =89 @5D;N:A, ACEVABL C 3;>BFV	5?@>EV4- =VABL B>2AB>3> :8H5G=8:C, :>?@>AB07, 1;N20==O*		8H:>20 =5?@>EV4=VABL* 014>@B*
5?0B>1V;V0@- =V @>7;048						>@CH5==O DC=:FV9 ?5GV=:8*, ?>@CH5==O C 40=8E ;01>@0B>@=8E 4>A;V465=L ?5GV=:>28E ?@>1*
1>:C H:V@8 V ?V4H:V@=8E B:0=8=			!CEVABL H:V@8	!25@1V6*, 28A8?0==O*	C;LB8-D>@ <=0 5@8B5 <0*, :@>?82'O=-:0* =01@O: 2V=:5*	:AD>;V0B82=89 45@<0B8B*

1>:C >?>@=>- @CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8 1>:C =8@>: B0 A5G>282V4=>W A8AB5<8			#B@C4=5=5 A5G>28?CA:0=- =O	0B@828?CA- :0==O		'O7>20 A;01:VABL * 8@:>20 =54>AB0B=VABL*
030;L=V @>7;048 V ?>@CH5==O C			V428I5=0 2B> <;N20-=VABL, ?5@8D5@8G- =89 =01@O:			

\*?VA;O@5TAB@0FV9=89 ?5@V>4.

"5@ABV.3 @>:8.

#<>28 715@V30==O. 15@V30B8 C =54>ABC?=>  
15@V30B8 ?@8 B5°!.

#?0:>2:0.> 10 B01;5B>: C 1;VAB5@V, ?> 1 01> ?> 3 1;VAB5@8 2 :0@B>==V9 :>@>1FV.

0B53>@VO 2V4?CA:C. □0 @5F5?B>

8@>1=8:. AB5;;0A \$0@<0 .@>? ..., V45@;0=48/Astellas Pharma Europe B. V.,the Netherlands.

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.%>35<0B 2, 7942 5??5;, V45@;0=48/Hogemaat 2, 7942 JG Meppel, the Netherlands.