

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

\$ □

(ZOFRAN□)

!::04:

4VNG0 @5G>28=0: >=40=A5B@>=;

1 <; @>7G8=C E;>@84C);

4>?>28=8: :8A;>B8 ;8<=>=>W <=>3V4@0B, =0B@VN F8B@0B, =0B@VN E;>@84, 2>40 4;O V=T:FV9.

V:0@AL:0 D>@<0. >7G8= 4;O V= T:FV9.

\$0@<0:>B5@0?52B8G=0 3@C?0. @>B81;N20;L=V 70A>18 B0 ?@5?0@0B8, I> CAC20NBL =C4>BC.
=B03>=VAB8 @5F5?B>@V2 A5@>B>=V=C (5³). >4 "!" 0401.

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

>:070==O.

C4>B0 V 1;N20==O, A?@8G8=5=V F8B>B>:A8G=>N EVB5@0?VTN B0 ?@><5=52>N B5@0?VTN.
@>DV;0:B8:0 B0 ;V:C20==O ?VA;O?5@0FV9=8E =C4>B8 V 1;N20==O.

@>B8?>:070==O.

0AB>AC20==O >=40=A5B@>=C @07>< 7 0?><@DV=C 3V4@>E;>@84>< ?@>B8?>:070=5, >A:V;L:8
A?>AB5@V30;8AO 28?04:8 A8;L=>W 0@B5@V0;L=>W 3V?>B5=7VW B0 2B@0B8 A2V4><>ABV ?V4
G0A AC3> 70AB>AC20==O.

V?5@GCB;82VABL 4>1C4L-O:>3> :>=5=B0 ?@5?0@0BC.

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

C4>B0 V 1;N20==O, A?@8G8=5=V EVB5@0?VTN B0 ?@><5=52>N B5@0?VTN

<5B>35==89 ?>B5=FV0; B5@0?VW @0:C 20@VNT 70;56=> 2V4 4>78 B0 :><1V=0FVW @568B5@0?VW
B0 ?@><5=52>W B5@0?VW. 81V@ @5687C20==O 70;568BL 2V4 BO6:>ABV 5<5B>35==>3> 2?;82C.

>@>A;V

<5B>35==0 EVB5@0?VO B0 ?@><5=520 B5@0?VO

5:><5=4>20=0 2=CB@VH=L>25==0 01> 2=CB@VH=L<O7>20 4>70 >D@0=C 8 <3 C 283;O4V
?>2V;L=>W V=T:FVW 2?@>4>26 =5<5=H5 =V6 30 A5:C=4, 157?>A5@54=L> ?5@54 ;V:C20==O
;O ?@>DV;0:B8:8 2V4AB@>G5=>3> 01> B@820;>3> 1;N20==O ?VA;O ?5@H8E 24 3>48= @5:>
<5=4CTBLAO ?5@>@0;L=5 01> @5:B0;L=5 70AB>AC20==O ?@5?0@0BC.

8A>:>5<5B>35==0 EVB5@0?VO (=0?@8::04 28A>:V 4>78 F8?;0B8=8)

>D@0= <>6=0 ?@87=0G0B8 C 283;O4V >4=>@07>2>W 4>78 8 <3 2=CB@VH=L>25==> 01>
2=CB@VH=L<O7>2> 157?>A5@54=L> ?5@54 EVB5@0?VTN. >78 ?>=04 8 <3 (4> 16 <3), <>6=0
70AB>A>2C20B8 ;8H5 C 283;O4V 2=CB@VH=L>25==>W V=DC7VW =0 50-100<; 0,9 % @>7G8=C
=0B@VN E;>@84C 01> V=H>3> 2V4?>2V4=>3> @>7G8==8:0 (482. =86G5 «=AB@C:FVW 4;O
70AB>AC20==O»); V=DC7VO <0T B@820B8 =5 <5=H5 15 E28;8=. 4=>@07>2C 4>7C 1V;LHC 70 16 <3
70AB>A>2C20B8 =5 <>6=0 (482. @>74V; «A>1;82>ABV 70AB>AC20==O»);
;O 28A>:>5<5B>35==>W EVB5@0?VW 8 <3 >D@0=C 01> <5=HC 4>7C =5 ?>B@V1=> @>72>48B8 B0
<>6=0 22>48B8 H;OE>< ?>2V;L=>W 2=CB@VH=L>25==>W 01> 2=CB@VH=L<O7>2>W V=T:FVW (=5
<5=H =V6 30 A5:C=4) 157?>A5@54=L> ?5@54 EVB5@0?VTN 7 ?>40;LH8< 42>@07>28<
2=CB@VH=L>25==8< 01> 2=CB@VH=L<□O7>28< 22545==O < 8 <3 G5@57 2 B0 4 3>48=8 01>
?>ABV9=>N V=DC7VTN 1 <3/3>48=C ?@>BO3>< 24 3>48=.

D5:B82=VABL >D@0=C ?@8 28A>:>5<5B>35==V9 EVB5@0?VW <>65 1CB8 ?V428I5=0 4>40B:>28<
>4=>@07>28< 2=CB@VH=L>25==8< 22545==O< 45:A0<5B07>=C =0B@VN D>AD0BC C 4>7V 20 <3
?5@54 EVB5@0?VTN.

;O ?@>DV;0:B8:8 2V4AB@>G5=>3> 01> B@820;>3> 1;N20==O ?VA;O ?5@H8E 24 3>48= @5:>
<5=4CTBLAO ?5@>@0;L=5 01> @5:B0;L=5 70AB>AC20==O ?@5?0@0BC.

VB8 B0 ?V4;VB:8 (2V:<> 2V4 6 17 @>:V2)

?54V0B@8G=V9 ?@0:B8FV >D@0= A;V4 22>48B8 H;OE< 2=CB@VH=L>25==>W V=DC7VW 2 25-50 <;
@>7G8=C 0,9 % @>7G8=C =0B@VN E;>@84C 01> V=H>3> 2V4?>2V4=>3> @>7G8==8:0 (482. =86G5
<=<AB@C:FVW 4;O 70AB>AC20==O) ?@>BO3<< =5 <5=H5 15 E28;8=. >7C ?@5?0@0BC <>6=0
@>7@0EC20B8 70 ?;>I5N ?>25@E=V BV;0 01><0A8 BV;0 48B8=8.

>7@0EC=>: 4>78 73V4=> 7 ?;>I5N ?>25@E=V BV;0 48B8=8

>D@0= A;V4 22>48B8 157?>A5@54=L> ?5@54 EVB5@0?VTN H;OE<< @07>2>W

2=CB@VH=L>25==>W V=□T:FVW C 4>7V 5 <3/<?, 2=CB@VH=L>25==0 4>70 =5 <0T ?5@528IC20B8
8 <3. '5@57 12 3>48= <>6=0 @>7?>G8=0B8 ?5@>@0;L=5 70AB>AC20==O ?@5?0@0BC, O:5 <>65
B@820B8 I5 5 4=V2. 5 ?5@528IC20B8 4>7C 4;O 4>@>A;8E.

>7@0EC=>: 4>78 73V4=> 7 <0A>N BV;0 48B8=8

>D@0= A;V4 22>48B8 157?>A5@54=L> ?5@54 EVB5@0?VTN H;OE<< @07>2>W

2=CB@VH=L>25==>W V=T:FVW C 4>7V 0,15 <3/:3. =CB@VH=L>25==0 4>70 =5 <0T ?5@528IC20B8 8
<3. # ?5@H89 45=L <>6=0 225AB8 I5 2 2=CB@VH=L>25==V 4>78 7 4-3>48==8< V=B5@20;> '5@57 12
3>48= <>6=0 @>7?>G8=0B8 ?5@>@0;L=5 70AB>AC20==O ?@5?0@0BC, O:5 <>65 B@820B8 I5 5 4=V2.
5 ?5@528IC20B8 4>7C 4;O 4>@>A;8E.

%2>@V ;VB=L>3> 2V:C

0FVT=B0< 2V:<> 2V4 65 @>:V2 2AV 4>78 4;O 2=CB@VH=L>25==8E V=T:FV9 A;V4 @>7G8=OB8 B0
22>48B8 ?@>BO3<< 15 E28;8=, ?@8 ?>2B>@=>AC20==V V=B5@20;

?0FVT=BV2 2V:<> 2V4 65 4> 74 @>:V2, ?>G0B:>20 4>70 >=40=A5B@>=C AB0=>28BL 8 <3 01> 16 <3,
WW 22>4OBL H;OE< 2=CB@VH=L>25==>W V=DC7VW ?@>BO3<< 15 E28;8=, O:C <>6=0

?@>4>268B8 22545==O< 2 4>7 ?> 8 <3 ?@>BO3<< 15 E28;8= 7 V=B5@20;<<

?0FVT=BV2 2V:<> 2V4 75 @>:V2 ?>G0B:>20 2=CB@VH=L>25==0 V=T:FVO >=40=A5B@>=C =5

?>28==0 ?5@528IC20B8 8 <3 7 V=DC7VTN 2?@>4>26 =5 <5=H5 15 E28;8=. VA;O ?>G0B:>2>W 4>78 C 8
<3 <>65 ?@>4>268B8 70AB>AC20==O 2 4>70<8 ?> 8 <3, O:V 22>4OBL H;OE< V=DC7VW ?@>BO3<<
15 E28;8= 7 V=B5@20;<<

0FVT=B8 7 =8@>:2>N =54>AB0B=VABN

5<0T =5>1EV4=>ABV C 77C20==O 01> H;OEC ?@87=0G5==O ?@5?0@0BC ?0FVT=B0< 7 ?>@CH5==O
< DC=:FVW =8@>:.

0FVT=B8 7 ?5GV=:>2>N =54>AB0B=VABN

?0FVT=BV2 7 ?>

0FVT=B8 7 ?>@CH5==O< <5B01>;V7:2V=C

5@V>4 =0?V2282545==O >=40=A5B@>=C C ?0FVT=BV2 7 ?>@CH5==O< <5B01>;V7:2V=C =5 7

2B>@=5 22545==O ?@872>48BL 4> B0:>W 6 A0<>W :=F5=B@0FVW ?@5?0@0BC, I> 9 C E2>@8E 7
=5?>@CH5=8< <5B01>;V7<>7C20==O 01> G0AB>B8 22545==O =5 ?>B@V1=0.

VA;O>?5@0FV9=V=C4>B0 V I;N20==O

>@>A;V

;O ?@>DV;0:B8:8 ?VA;O>?5@0FV9=8E =C4>B8 V 1;N20==O @5:<5=4>20=0 4>70 >D@0=C AB0=>28BL
4 <3 C 283;O4V >4=>@07>2>W 2=CB@VH=L<<07>2>W 01> ?>2V;L=>W 2=CB@VH=L>25==>W
V=T:FVW ?V4 G0A 22545==O 2 =0@>:7.

;O ;V:C20==O ?VA;O>?5@0FV9=8E =C4>B8 V 1;N20==O @5:<5=4>20=0 @07>20 4>70 >D@0=C

AB0=>28BL 4 <3 C 283;O4V 2=CB@VH=L<<07>2>W 01> ?>2V;L=>W 2=CB@VH=L>25==>W V=T:FVW.
VB8 B0 ?V4;VB:8 (2V:<> 2V4 1 17 @>:V2)

;O ?@>DV;0:B8:8 V ;V:C20==O ?VA;O>?5@0FV9=8E =C4>B8 V 1;N20==O C 4VB59, O:8E >?5@CNBL
?V4 7030;L=>N 0=5AB57VTN, >D@0= <>6=0 22>48B8 C 4>7V 0,1 <3/:3 <0A8 BV;0 (<0:A8<0;L=> 4> 4
<3) H;OE<< ?>2V;L=>W 2=CB@VH=L>25==>W V=T:FVW (=5<5=H5 30 A5:C=4) 4>, ?V4 G0A,

?VA;O 22545==O C =0@>:7 01> ?VA;O >?5@0FVW.

%2>@V ;VB=L>3> 2V:C

>A2V4 70AB>AC20==O >D@0=C 4;O ?@>DV;0:B8:8 V ;V:C20==O ?VA;O>?5@0FV9=8E =C4>B8 V
1;N20==O C ;N459 ;VB=L>3> 2V:C >1<565=89, >4=0: >D@0= 4>1@5 ?5@5=>A8BLAO E2>@8<8,
AB0@H8<8 65 @>:V2, O:V >B@8B5@0?VN.
0FVT=B8 7 =8@:>2>N =54>AB0B=VABN
5<0T =5>1EV4=>ABV C 77C20==O 01> H;OEC ?@87=0G5==O ?@5?0@0BC ?0FVT=B0< V7 ?>@CH5==O
< DC=:FVW =8@>:.

0FVT=B8 7 ?5GV=:>2>N =54>AB0B=VABN

?0FVT=BV2 7 ?>

0FVT=B8 7 ?>@CH5==O< <5B01>;V7:2V=C

5@V>4 =0?V2282545==O >=40=A5B@>=C C AC1T:BV2 7 ?>@CH5==O< <5B01>;V7:2V=C =5 72B>@=5
22545==O ?@872>48BL 4> B0:>W 6 :=F5=B@0FVW ?@5?0@0BC, I> 9 C E2>@8E 7 =5CH:>465=8<
<5B01>;V7<>7C20==O 01> G0AB>B8 22545==O =5 ?>B@V1=0.

=AB@C:FVO 4;O 70AB>AC20==O.

D@0=><=5 =A5@20=BV2 V WE =5>1EV4=> 28:>@8AB>2C20B8 =5309=> ?VA;O @>7:@8BBO;

@>7G8=, I> 70;8H82AO, ?>B@V1=> 7=8I8B8.

D@0=><=5 <>6=0 02B>;02C20B8.

!C

>7G8=8 4;O 2=CB@VH=L>25==>3> 2;820==O ?>B@V1=> 3>BC20B8 157?>A5@54=L> ?5@54
V=DC7VTN. @>B5 2AB0=>2;5=>, I> @>7G8= >=40=A5B@>=C 715@V30T AB01V;L=VABL ?@>BO3<

7 4=V2 ?@8 :V<=0B=V9 B5 25 □) ?@8 45==> 2 E>;>48;L=8:C ?@8 @>7G8=5==V 2 B0:8E
A5@54>28I0E: 0,9 % @>7G8= =0B@VN E;>@84C, @>7G8= 3;N:>78 5 %, @>7G8= <0=VB>;C 10 %,
@>7G8= V=35@0, 0,3 % @>7G8= :0;VN E;>@84C V 0,9 % @>7G8= =0B@VN E;>@84C, 0,3 % @>7G8=
:0;VN E;>@84C V @>7G8= 3;N:>78 5 %.

AB0=>2;5=>, I> >=40=A5B@>= 715@V30T AB01V;L=VABL B0:>6 ?@8 28:>@8AB0==V ?>;V5B8;5=>28E

V A;;O=8E D;0:>=V2. C;> ?>:070=>, I> >=40=A5B@>=, @>72545=89 0,9 % E;>@84< =0B@VN 01> 5 %
3;N:>7>N, 715@V30T AB01V;L=VABL C ?>;V?@>?V;5=>28E H?@8F0E. >2545=> B0:>6, I>

AB01V;L=VABL C ?>;V?@>?V;5=>28E H?@8F0E 715@V30TB LAO ?@8 @>72545==V >=40=A5B@>=C
V=H8<8 @5:><5=4>20=8<8 @>7G8=0<8.

@07V =5>1EV4=>ABV B@820;>3> 715@V30==O ?@5?0@0BC @>7G8=5==O A;V4 ?@>2>48B8 C
2V4?>2V4=8E 0A5?B8G=8E C<>20E.

!C

>D@0= <>6=0 ?@87=0G0B8 C 283;O4V 2=CB@VH=L>25==>W V=DC7VW 7V H284:VABN 1<3/3>48=C.

'5@57 Y-?>4V1=89 V='T:B>@ @07< V7 >D@0=>< ?@8 :=F5=B@0FVW >=40=A5B@>=C 2V4 16 4>
160

- F8A?;0B8= C :=F5=B@0FVW 4> 0,48 <3/<; ?@>BO3>< 1-8 3>48=;
- 5-DB>@C@0F8; C :=F5=B@0FVW 4> 0,8 <3/<; (=0?@8;;04 2,4 3 C 3 ; 01> 400<3 C 500 <); 7V
H284:VABN =5 1V;LH5 20<;/3>48=C. V;LH 28A>:0 :=F5=B@0FVO 5-DB>@C@0F8;C <>65
A?@8G8=8B8 ?@5F8?VB0FVN >=40=A5B@>=C. >7G8= 4;O V=DC7V9 5-DB>@C@0F8;C <>65 0,045
% E;>@84C <03=VN =0 4>?>2=5==O 4> V=H8E =0?>2=N20GV2, I> T AC
- :0@I>?;0B8= C :=F5=B@0FVW 2V4 0,18 <3/<; 4> 9,9 <3/<; (=0?@8;;04 2V4 90 <3 2 500 <; 4> 990 <3
2 100 <); ?@>BO3>< 10-60 E28;8=;
- 5B>?>784 C :=F5=B@0FVW 2V4 0,14 <3/<; 4> 0,25 <3/<; (=0?@8;;04 2V4 72 <3 2 500 <; 4> 250 <3 2 1
); ?@>BO3>< 30-60 E28;8=;
- F5DB07848< C 4>7V 2V4 250 <3 4> 2 3, @>72545=89 C 2>4V 4;O V='T:FV9 (=0?@8;;04 2,5 <; =0 250
<3 01> 10 <; =0 2 3 F5DB0784825==>W 1>;NA=>W V='T:FVW ?@>BO3>< 5 E28;8=;
- F8;;>D>AD0 C 4>7V 2V4 100 <3 4> 1 3, @>72545=89 C 2>4V 4;O V='T:FV9 (5 <; =0 100 <3
F8;;>D>AD025==>W 1>;NA=>W V='T:FVW ?@>BO3>< 5 E28;8=;
- 4>:A>@CIVF8= C 4>7V 2V4 10 <3 4> 100 <3, @>72545=89 C 2>4V 4;O V='T:FV9 (5 <; =0 10 <3
4>:A>@C1VF8=C), C 283;O4V 2=CB@VH=L>25==>W 1>;NA=>W V='T:FVW ?@>BO3>< 5 E28;8=;
- 45:A0<5B07>= C 4>7V 20 <3, C 283;O4V ?>2V;L=>W 2=CB@VH=L>25==>W V='T:FVW ?@>BO3><
2-5 E28;8= (?@8 >4=>G0A=> 50-100 <; V='T:FV9=>3> @>7G8=C), ?@>BO3>< ?@81;87=> 15
E28;8=. A;V;L:8 40=V ?@5?0@0B8 T AC7G8=V :=F5=B@0FVW 45:A0<5B07>=C D>AD0BC (C D>@
W A>;V) 1C4CBL AB0=>28B8 2V4 32 2,5 <3 2 1 <;, 0 >=40=A5B@>=C 2V4 8 1 <3 2 1 <;.

>1VG=V @50:FVW.

>1VG=0 4VO, V=D>@<0FVO ?@> O:C =02545=0 =86G5, ;:0A8DV:>20=0 70 >@30=0<8 V A8AB5<0<8 B0
70 G0AB>B>N WW 28=8:=5==O. 0 G0AB>B>N 28=8:=5==O @>7?>4V;5=0 =0 B0:V :0B53>@VW: 4C65
G0AB> (≥1/10), G0AB> (≥1/100 B0 <1/10), =5G0AB> (≥1/1000 B0 <1/100), @V4:> (≥1/10000 B0 <1/1000),
4C65 @V4:> (<1/10000).

I>:C VW A8AB5<8:

@V4:>: @50:FVW 3V?5@GCB;82>ABV =5309=>3> B8?C, V=:>;8 BO6:V, 06 4> 0=0DV;0:AVW.

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

4C65 G0AB>: 3>;>2=89 1V;L;

=5G0AB>: AC4><8, @CE>2V ?>@CH5==O (2;:NG0NG8 5:AB@0?V@0:C;>38@=89 :@87, 48AB>=VG=V
@50:FVW V 48A:V=57VO 157 ABV9:8E ;:V=VG=8E =0A;V4:V2);

@V4:>: 70?0<>@>G5==O ?5@5206=> ?V4 G0A H284:>3> 2=CB@VH=L>25==>3> 22545==O
?@5?0@0BC.

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

@V4:>: A:>@<8=CIV 7>@>2V @>7;048 (?>G0E), 3>;>2=8< G8=>< ?V4 G0A 2=CB@VH=L>25==>3>
22545==O;

4C65 @V4:>: <8=CIO A;V?>B0, 3>;>2=8< G8=>< ?V4 G0A 2=CB@VH=L>25==>3> 70AB>AC20==O. #
1V;LH>ABV 28?04:V2 A;V?>B0 <8=0T ?@>BO3>< 20 E28;8=.

I>:C A5@FO:

=5G0AB>: 0@8BST 01> 157 =5W), 1@048:0@4VO;

@V4:>: ?>4>265==O V=B5@20;C QT (2;:NG0NG8 B@5Torsade de Pointes).

I>:C AC48=:

G0AB>: 2V4GCBBO B5?;0 01> ?@8?;82V2;

=5G0AB>: 3V?>B5=7VO.

I>:C 48E0;L=>W A8AB5<8 B0 >@30=V2 3@C4=>W ?>@>6=8=8:

=5G0AB>: 38:02:0.

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

G0AB>: 70?>@.

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

=5G0AB>: 157A8<=5 ?V428I5==O ?>:07=8:V2 DC=:FVW ?5GV=:8.

&V 28?04:8 A?>AB5@V30NBLAO 3>;>2=8< G8=>< C E2>@8E, O:V ;V:CNBLAO EVB5@0?52B8G=8<8
?@5?0@0B0<8, I>

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

C65 @V4:>: B>:A8G=V 28A8?0==O, 2 B>:A8G=89 5?V45@<0;L=89 =5:@>;V7.

030;L=V @>7;048

'0AB>: 25==>3> 22545==O.

0 40=8<8 ?VA;O@5TAB@0FV9=>3> A?>AB5@565==O ?>2V4<;O;>AL ?@> B0:V ?>1VG=V @50:FVW.

I>:C A5@F52>-AC48==>W A8AB5<8: 1V;L B0 48A:>@B C 3@C4OE, 5:AB@0A8AB>;8, B0EV:0@4VO,
2;:NG0NG8 H;C=>G:>2C B0 =04H;C=>G:>2C B0EV:0@4VN, DV1@8;OFVN ?5@54A5@4L, 2V4GCBBO

A5@F518BBO, A8=:>?5, 7

50:FVW 3V?5@GCB;82>ABV: 0=0DV;0:B8G=V @50:FVW, 0=V>=52@>B8G=89 =01@O.;, 1@>=E>A?0<,
0=0DV;0:B8G=89 H>;, A25@1V6, H:V@=V 28A8?0==O, :@>?82O=:0.

I>:C =5@2>2>W A8AB5<8: ?>@CH5==O E>48, E>@5O, ;:=CA, =5230<>2=VABL, 2V4GCBBO

?5GV==O, ?@>B@C7VO O78:0, 48?;>?VO, ?0@5AB57VO.

030;L=V ?>@CH5==O B0 ?V428I5==O B5G5@2>=V==O, ?5GV==O 2

=H5: 3V?>:0;VT

5@54>7C20==O.

0=8E ?@> ?5@54>7C20==O >D@0=C =54>AB0B=L>. # 1V;LH>ABV 28?04:V2 A8<8 AE>6V =0 BV, I>
>?8A0=V C ?0FVT=V2, O:8< 22>48;8 @5:><5=4>20=V 4>78 (482. @>74V; <<>1VG=V @50:FVW»).

=40=A5B@>= ?>4>26CT V=B5@20; QT C 4>7>70;56=V9 D>@7C20==O @5:><5=4CTBLAO ?@>2545==O
-<>=VB>@8=3C.

!5@54 ?@>O2V2 ?5@54>7C20==O ?>2V4<;O;>AL ?@> B0:V O: 7>@>2V @>7;048, 70?>@ BO6:>3>

ABC?5=O, 3V?>B5=7VO, 207>2030;L=V ?@>O28 V7 B@0=78B>@=>N AV 1;>:04>N ABC?5=O. # 2AVE
28?04:0E FV O28I0 ?>2=VABN <8=0;8.

!75F8DVG=>3> 0=B84>BC =5 VA=CT, B>7C20==O =5>1EV4=> 70AB>A>2C20B8 A8<0B8G=C B0
?V4B@8
0AB>AC20==O V?5:0:C0=8 4;O ;V:C20==O ?5@54>7C20==O >=40=A5B@>=C =5 @5:<5=4CTBLAO,
>A:V;L:8 WW 4VO =5 <65 28O28B8AO G5@57 0=B85<5B8G=89 2?;82 >D@0=C.

0AB>AC20==O 2 ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

57?5:0 70AB>AC20==O >D@0=C C ?5@V>4 203VB=>ABV 4;O ;N48=8 =5 2AB0=>2;5=0. V4 G0A
5:A?5@8<5=B0;L=8E 4>A;V465=L =0 B20@8=0E >D@0= =5 ?>@CHC202 @>728B>: 5<1@V>=0 01>
?;>40 V =5 2?;8202 =0 ?5@51V3 203VB=>ABV, ?5@8- B0 ?>AB=0B0;L=89 @>728B>:. @>B5, >A:V;L:8
4>A;V465==O =0 B20@8=0E =5 702648 ?@>3=>AB8G=V 4;O ;N48=8, >D@0= =5 @5:<5=4CTBLAO
70AB>A>2C20B8 C ?5@V>4 203VB=>ABV.
5:A?5@8<5=B0;L=8E 4>A;V465==OE 1C;> ?>:070=>, I> >=40=A5B@>= ?@>=8:0T C 3@C4=5 <>;>:
B20@8=. # @07V =5>1EV4=>ABV 70AB>AC20==O ?@5?0@0BC A;V4 ?@8?8=8B8 3>4C20==O 3@C44N.

VB8.

0AB>A>2CNBL 4VBO< 2V:< 2V4 6 B5@0?VW) B0 2V:< 2V4 1 DV;0:B8:8 V ;V:C20==O
?VA;O>?5@0FV9=8E =C4>B8 V 1;N20==O).

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

@8 ;V:C20==V ?0FVT=BV2 V7 ?@>O20<8 3V?5@GCB;82>ABV 4> V=H8E A5;5:B82=8E 0=B03>=VABV2
5"-@5F5?B>@V2 A?>AB5@V30;8AO @50:FVW 3V?5@GCB;82>ABV.
=40=A5B@>= C 4>7>70;56=V9 D>@4>26CT V=B5@20; QT (482. @>74V; «\$0@<0:>;>3VG=V
2;0AB82>ABV»). >40B:>2> 70 40=8<8 ?VA;O<0@:5B8=3>2>3> A?>AB5@565==O 1C;8 ?>2V4<;5==O
?@> 28?04:8 B@5Torsade de Pointes) ?@8 70AB>AC20==V >=40=A5B@>=C. !;V4 C=8:0B8
70AB>AC20==O >=40=A5B@>=C C ?0FVT=BV2 7 2@>465=8< A8=4@<<< ?>4>265==O QT.
=40=A5B@>= A;V4 70AB>A>2C20B8 7 >15@56=VABN 4;O ;V:C20==O ?0FVT=BV2, O:V<0NBL 01> C
O:8E <>65 @>728=CB8AL ?>4>265==O V=B5@20;C QT, 2.;NG0NG8 ?0FVT=BV2 7 ?>@CH5==O<
5;5:B@>;VB=>3> 10;0=AC, 70ABV9=>N A5@F52>N =54>AB0B=VABN, 1@04V0@8BQT 01>
?>@CH5==O 5;5:B@>;VB=>3> 10;0=AC. 5@54 ?>G0B:<< 70AB>AC20==O A;V4 A:>@53C20B8
3V?>:0;VT<03=VT
VA;O>4=>G0A=>3> 70AB>AC20==O >=40=A5B@>=C B0 V=H8E A5@>B>=V=5@3VG=8E
?@5?0@0BV2 1C2 >?8A0=89 A5@>B>=V=>289 A8=4@<< (482. @>74V; «70T<>4VO 7 V=H8<8
;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). !:I> >4=>G0A=5 ;V:C20==O >=40=A5B@>=<< B0
V=H8<8 A5@>B>=V=5@3VG=8<8 ?@5?0@0B0<8 ;;V=VG=> >1@3C=B>20=>, @5:<5=4CTBLAO
2V4?>2V4=5 A?>AB5@565==O ?0FVT=B0.
A:V;L:8 >=40=A5B@>= ?>A;01;NT ?5@8AB0;LB8:C :8H5G=8:C, ?>B@V1=89 @5B5;L=89 =03;O4 70
?0FVT=B0<8 7 >7=0:0<8 ?V43>AB@>W =5?@>EV4=>ABV :8H5G=8:C ?V4 G0A 70AB>AC20==O
>D@0=C.
?0FVT=BV2, O:8< ?@>2>48BLAO EV@C@3VG=5 2B@CG0==O 2 045=>B>=78;O@=V9 >1;0ABV,
70AB>AC20==O >=40=A5B@>=C 4;O ?@>DV;0:B8:8 =C4>B8 B0 1;N20==O <>65 <0A:C20B8 28=8:=5==O
:@>2>B5GV. ">@V ?V4;O30NBL @5B5;L=>AC20==O >=40=A5B@>=C.

**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.**

A8E<>B>@=V B5AB8 ?>:070;8, I> >=40=A5B@>= =5 2?;820T =0 740B=VABL :5@C20B8<5E0=V7<0<8
V =5 G8=8BL A540B82=>W 4VW, 0;5 A;V4<0B8 =0 C207V ?@>DV;L ?>1VG=8E 4V9 ?@5?0@0BC ?@8
28@VH5==V ?8B0==O ?@> 740B=VABL :5@C20B8 02B>B@0A?>@B< 01> @>1>BV 7 V=H8<8
<5E0=V7<0<8.

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

=40=A5B@>= =5 ?@8A:>@NT V =5 30;L<, 0;D5=B0=V;<<, B@0<04>;<<, <>@DV=<<;V3=>:0W=<<,
BV>?5=B0;>< 01> ?@>?>D>;>

=40=A5B@>=<5B01>;V7CTBLAO @V7=><0=VB=8<8 D5@<5=B0<8 F8B>E@><>CYP3A4, CYP2D6 B0
CYP1A2. 0240:8 @V7=><0=VB=>ABV D5@<5=BV2 <5B01>;V7=40=A5B@>=C 30;L 7<5=H5==O
0:B82=>ABV >4=>3> 7 =8E (=0?@8:;04 35=5B8G=89 45DVF8B CYP2D6) C 728G09=8E C<>20E :> 2?;82
=0 7030;L=89 ;;V@5=A :@50B8=V=C 1C45 =57=0G=8
>15@56=VABN A;V4 70AB>A>2C20B8 >=40=A5B@>= @07< 7 ;V:0@AL:8<8 70A>10<8, I>
?>4>26CNBL V=B5@20; QT B0/01> A?@8G8=ONBL 4> ?>@CH5==O 5;5:B@>;VB=>3> 10;0=AC (482.
@>74V; «A>1;82>ABV 70AB>AC20==O»).

?><>@DV=
0AB>AC20==O >=40A5B@>=C @07<< 7 0?><>@DV=C 3V4@>E;@84<< ?@>B8?>:070=5, >A:V;L:8
A?>AB5@V30;8AO 28?04:8 A8;L=>W 3V?>B5=7VW B0 2B@0B8 A2V4<>ABV ?V4 G0A AC3>
70AB>AC20==O.

\$5=VB>W=, :0@10<075?V= V @8D0
?0FVT=BV2, O:V ;V:CNBLAO ?>B5=7V9=8<8 V=4C:B>@0<8 CYP3A4 (=0?@8:;04 D5=VB>W=><,
:0@10<075?V=>< V @8D0<), ;;V@5=A >=40=A5B@>=C 71V;LHCTBLAO V 9>3> :>=F5=B@0FVO C
:@>2V 7<5=HCTBLAO.

!5@>B>=V=5@35B8:8 (=0?@8:;04, !! B0 □□ !)
!5@>B>=V=>289 A8=4@<< (2;;NG0NG8 ??A8EVG=>3> AB0BCAC, 2535B0B82=>W =5AB01V;L=>ABV
V =5@2>2>-<O7>28E ?>@CH5=L) 1C2 >?8A0=89 ?VA;O>4=>G0A=>3> 70AB>AC20==O
>=40=A5B@>=C B0 V=H8E A5@>B>=V=5@3VG=8E ?@5?0@0BV2, C B> V=3V1VB>@V2 72>@>B=>3>
70E>?;5==O A5@>B>=V=C (!) B0 V=3V1VB>@V2 72>@>B=>3> 70E>?;5==O A5@>B>=V=C B0
=>@04@5=0;V=C (□ !)(482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

"@0<04>;
0 40=8<8 =525;8:>W :V;L:>ABV ;;V=VG=8E 4>A;V465=L, >=40=A5B@>= <>65 7<5=HC20B8
0=0;35B8G=89 5D5:B B@0<04>;C.
0AB>AC20==O >D@0=C 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, I> ?>4>26CNBL V=B5@20; QT, <>65
A?@8G8=OBL 4>40B:>25 ?>4>265==O FL>3> V=B5@20;C. !CAC20==O >D@0=C 7 :0@4V>B>:A8G=8<8
;V:0@AL:8<8 70A>10<8 (=0?@8:;04, 0=B@0F8:;V=0<8) <>65 71V;LH8B8 @878: 28=8:=5==O 0@8B74V;
«A>1;82>ABV 70AB>AC20==O»).

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

\$0@<0:>48=0
=40=A5B@>= A8;L=>4VNG89 28A>:>A5;5:B82=89 0=B03>=VAB 5"; (A5@>B>=V=>28E) @5F5?B>@V2.
@5?0@0B ?>?5@546CT 01> CAC20T =C4>BC V 1;N20==O, I> A?@8G8=ONBLAO F8B>B>:A8G=>N EV
B5@0?VTN B0/01> ?@<<5=52>N B5@0?VTN, 0 B0:>6 ?VA;O>?5@0FV9=V =C4>BC V 1;N20==O. 5E0=V7
< 4VW >=40=A5B@>=C 4> :V=FO =5 7'OA>20=89. >6;82>, ?@5?0@0B 1;>:CT 28=8:=5==O 1;N20;L=>3>
@5D;5:AC, 28O2;ONG8 0=B03>=VAB8G=C 4VN 2V4=>A=> 5"-@5F5?B>@V2, O:V ;>:0;V7CNBLAO C
=59@>=0E O: ?5@8D5@8G=>W, B0: V F5=B@0;L=>W =5@2>2>W A8AB5<8. @5?0@0B =5 7<5=HCT
?A8E<@=>W 0:B82=>ABV ?0FVT=B0 V =5 G8=8BL A540B82=>3> 5D5:BC.

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

@8 2=CB@VH=L<<□O7>2> 22545==V ?V:>20 :>=F5=B@0FVO C ?;072V ?@>BO3<< 10 E28;8=. 1T<
@>7?>4V;C ?VA;O ?0@5=B5@0;L=>3> 22545==O C 4>@>A;8E AB0=>28BL140 ;, A=>2=0 G0AB8=0
22545=>W 4>78 ?V440TBLAO <5B01>;V748BLAO <5=H5 5 % ?@5?0@0BC. 5@V>4 =0?V2282545==O
?@81;87=> 3 3>48=8 (C E2>@8E ;VB=L>3> 2V:C 5 3>48=). 2O7C20==O 7 1V;:0<8 ?;07<8 70-76 %.
?0FVT=BV2 7 =8@:>2>N =54>AB0B=VABN ?>3> ABC?5=O (;V@5=A :@50B8=V=C 15-60<;/E2) 7
<5=HCNBLAO O: A8AB5<=89 ;;V@5=A, B0: V >1T< @>7?>4V;C >=40=A5B@>=C, @57C;LB0B<< G>3>
T =57=0G=5 V ;;V=VG=> =57=0GCI5 71V;LH5==O ?5@V>4C =0?V2282545==O ?@5?0@0BC. \$0@
<0:>:V=5B8:0 >=40=A5B@>=C ?@0:B8G=> =5 72>N =54>AB0B=VABN B06:>3> ABC?5=O, O:V
7=0E>4OBLAO =0 E@>=VG=> 7<5=HCTBLAO 7V 71V;LH5==O< ?5@V>4C =0?V2282545==O (15-32
3>48=).

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

A=>2=V DV78:>-EVABV: ?@>7>@0 15710@2=0 @V48=0, ?@0:B8G=> =5 :.

>D@0= =5 <6=0 70AB>A>2C20B8 2 >4=> V=DC7V9=>7G8=V @07>< 7 V=H8<8 ;V:0@AL:8<8 70A>10
<8. >D@0= C D>@ T:FV9 <6=0 ?>T4=C20B8 ;8H5 7 @5:><5=4>20=8<8 @>7G8=0<8 4;O V=DC7V9 (482.
@>74V; «!>AV1 70AB>AC20==O B0 4>78»).

"5@ABV.

3 @>:8.

#<28 715@V30==O.

15@V30B8 ?@8 B5 2 7>2=VH=V9 ?0GFV 4;O 70E8ABC 2V4 4VW A2VB;0. 15@V30B8 C =54>ABC?=>

#?0:>2:0.

2 <; 01> 4 <;; ?> 5 0==V9 :>@>1FV.

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

0 @5F5?B>

8@>1=8:.

;0:A>!

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VAF57=0E>465==O.

;0:A>!2V=AV0;L A>;0=0 90, (@09>= !0= >;>) 43056 ">@@@V;5 (0@<0), B0;VO/

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Italy.