

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

"□□
(MOTINOL)

!;:04 ;V:0@AL:>3> 70A>1C:

4VNG0 @5G>28=0: 4>=;
1 B01;5B:0 @=C <0;50BC;
4>?>28=8: :@>E<0;L :C:C@C47O=89, =0B@VN 4>:C70B 85 % =0B@VN 15=7>0B 15 % (211), F5;N;>70
:@8AB0;VG=0, ;0:B>78 <=>3V4@0B, ?>2V4=>, <03=VN AB50@0B, =0B@VN :@>A:0@<5;>70;
A:;04 >1>;>=:8: 3V?@<5;>70, 3V4@>:A8?@>?V;F5;N;>70, B8B0=C 4V>:A84 (171), ?>;V5B8;5=3;V:>;L.

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

"01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 1V;>3> 01> 7;53:0 :@5<2>3> :>;L>@C, 42>>?C;>;V, :@C3;>W
D>@<8 7 3;045=L:8< ?>:@8BBO4=>3> 1>:C B01;5B:8 =0=5A5=V 2V418B>; :>3>B8?C « » V F8D@0 «10»,
7 V=H>3> 1>:C B01;5B:0 3;045=L:0.

0720 V 465==O 28@>1=8:0.

\$0@<0A09=A =:., 6111 >O;<0C=B 25=N, 100, >=@50;L, 2515: 4 2"4, 0=040 /
Pharmascience Inc., 6111 Royalmount Avenue 100, Montreal, Quebec H4P 2T4, Canada.

\$0@<0:>B5@0?52B8G=0 3@C?0. !B8@8 ?5@8AB0;LB8:8. >4 "I A03F 03.

\$0@<0:>48=0

>= 0=B03>=VAB 4>D0B81;N2>B=8<8 2;0AB82>ABO<8. >= =57=0G=>N N ?@>=8:0T :@V7L 35
<0B>5=F5D0;VG=89 10@T@. 0AB>AC20==O 4>=C 4C65 @V4:> AC?@>2>46CTBLAO 5:AB@0?V@0
;0:B8=C 7 3V?>DV70. >3> ?@>B81;N2>B=0 4VO, <>6;82>, 7C<>2;5=0 ?>T4=0==O< ?5@8D5@8G=>W
(30AB@>:V=5B8G=>W) 4VW B0 0=B03>=V7 @5F5?B>@V2 4>D0=V E5<>@5F5?B>@V2, I>
7=0E>48BLAO ?>70 35<0B>5=F5D0;VG=8< 10@T@< C 704=V9 4V;O=FV (area postrama).

>A;V465==O =0 B20@8=0E, 0 B0:>6 =87L:V :>=F5=B@0FVW, I> 287=0G0;8AL C<>7:C, 2:07CNBL =0
?5@5206=> ?5@8D5@8G=C 4VN 4>=C =0 @5F5?B>@8 4>D0

>A;V465==O C ;N48=8 ?>:070;8, I> ?@8 70AB>AC20==V 2=CB@VH=L> 4>= ?V428ICT B8A: C =86=VE
2V44V;0E AB@02>E>4C, ?>:@0ICT 0=B@>4C>45=0;L=C <>B>@8:C B0 ?@8A:>@NT 282V;L=5==O
H;C=:0. >= =5 2?;820T =0 H;C=:>2C A5:@5FVN.

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

>= H284:> 01A>@1CTBLAO ?@8 ?5@>@0;L=>AO30TBLAO ?@81;87=> G5@57 60 E2. 87L:0 01A>;NB=0
1V>4>ABC?>VABL ?5@>@0;L=>3> 4>=C (?@81;87=> 15 %) 7C<>2;5=0 5:AB5=A82=8< <5B01>;V7<<<
?5@H>3> ?@>E>465==O C ABV=FV :8H5G=8:C B0 C ?5GV=FV. %>G0 C 74>@>28E ;N459

1V>4>ABC?>VABL 4>=C 71V;LHCTBLAO ?@8 ?@89>@8< 7V A:0@30<8 H;C=:>2>-.8H:>2>3>

E0@0:B5@C A;V4 ?@89<0B8 4>= 70 15-30 E28;8= 4> W48. =865=0 :8A;>B=VABL H;C=:0 7<5=HCT

01A>@1FVN 4>=C. @8 ?5@>@0;L=>

@8 ?5@>@0;L=>= =5 0:C1 30 <3 =0 45=L 1C2 <0965 B0:8< A0<8<, O: ?VA;O ?@89>W 4>78 (18 =3/<.); >=
=0 91-93 % 7207CTBLAO 7 1V;:0<8 ?;07<8 :@>2V. >A;V465==O @>7?>4V;C 4>=C ?>:070;8 9>3> 7=0G=89

@>7?>4V; C B:0=8=0E, 0;5 =87L:C :>=F5=B@0FVN 2 <>7:C.

>= H284:> B0 5:AB5=A82=> <5B01>;V7CTBLAO C ?5GV=FV H;OE<< 3V4@>:A8;N20==O B0
N-450;;V;C20==O.

82545==O V7 A5G5N B0 :0;< AB0=>28BL 2V4?>2V4=> 31 % B0 66 % 2V4 ?5@>@0;L=>W 4>78.

84V;5==O ?@5?0@0BC C =5728BL =525;8:89 2V4A>B>: (10 % 7 :0;< B0 ?@81;87=> 1 % V7 A5G5N).

5@V>4 =0?V2282545==O 7 ?;07<8 :@>2V ?VA;O ?@89>2>W 4>78 AB0=>28BL 7-9 3>48= C 74>@>28E

4>1@>2>;LFV2, 0;5 C E2>@8E 7 B06:>N =8@:>2>N =54>AB0B=VABN 2V= ?>4>265=89.

>:070==O 4;O 70AB>AC20==O.

;O ?>;53H5==O A8B8 B0 1;N20==O.

@>B8?>:070==O.

>B8=>; ?@>B8?>:070=89:

- E2>@8< 7 ?V428I5=>N GCB;82VABN 4> ?@5?0@0BC 01> 4> 4>?>28=;
- E2>@8< 7 ?@>;0:B8=-A5:@5B>@=>N ?CE;8=>N 3V?>DV70 (?@>;0:B8=><>N);
- E2>@8< 7 BO6:8<8 01> ?>
- E2>@8< 7 ?>4>265==O< V=B5@20;V2 A5@F52>W ?@>2V4=>ABV, 7>:@5<0 QTc, E2>@8< 7V 7=0G=8<8 ?>@CH5==O<8 10;0=AC 5;5:B@>;VBV2 01> 7 D>=>28<8 E2>@>10<8 A5@FO, B0:8<8 O: 70ABV9=0 A5@F520 =54>AB0B=VABL (482. @>74V; «A>1;82>ABV 70AB>AC20==O»);
- E2>@8< 7 ?5GV=:>2>N =54>AB0B=VABN;
- O:I> AB82>W DC=:FVW H;C=:0 <>65 1CB8 =5157?5G=>N, =0?@8:;04 ?@8 H;C=:>2>-.8H:>2>W :@>2>B5GV, <5E0=VG=V9 =5?@>EV4=>ABV 01> ?5@D>@0FVW;
- C @07V >4=>G0A=>3> 70AB>AC20==O :5B>:>=07>;C, 5@8B@> V=H8E A8;L=>4VNG8E V=3V1VB>@V2 CYP3A4;
- C @07V >4=>G0A=>3> 70AB>AC20==O ;V:0@AL:8E 70A>1V2, O:V ?>4>26CNBL V=B5@20;QT, B0:8E O: D;C:>=07>;, 5@8B@>=07>;, ?5@>@0;L=89 :5B>:>=07>;, ?>A0:>=07>;, @8B@>=02V@, A0:2V=02V@, B5;0?@52V@, 2>@8:>=07>;, :0@8B@>40@>=, B5;VB@>74V;8 «A>1;82>ABV 70AB>AC20==O» B0 <70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

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

>= 5 @5:><5=4CTBLAO ?@8 70E8BC20==V.

>= A;V4 70AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0< ;VB=L>3> 2V:C B0 ?0FVT=B0< 7 =0O2=8< 70E2>@N20==O< A5@FO 01> V7 70E2>@N20==O< A5@FO 2 0=0<=57V.

!5@F52>-AC48==V 5D5:B8. □>= 1C2 ?>2'O70=89 7 ?@>;>=30FVTN V=B5@20;C QT =0 . V4 G0A ?>AB <0@:5B8=3>2>3> A?>AB5@565==O 70DV:A>20=> 4C65 @V4:VA=V 28?04:8 ?@>;>=30FVWQT B0 B@V?>BV==O<5@5EBV==O H;C=>G:V2 C ?0FVT=BV2, O:V ?@89<0;8 4>=. &V ?0FVT=B8 <0;8 B0:>6 G8==8:8 @878:C, 5;5:B@>;VB=V ?>@CH5==O 01> ?@>E>48;8 AC?CB=N B5@0?VN.

V4?>2V4=> 4> @5:><5=40FV9 !14, 1C;> ?@>2545=> 4>A;V465==O 7 @5B5;L=8< 282G5==O< V=B5@20;C QT C 74>@>28E >AV1. >4>265==O V=B5@20;CQT, O:5 A?>AB5@V30;8 C 4>A;V465==V ?@8 70AB>AC20==V 4>=C C 728G09=8E B5@0?52B8G=8E 4>70E (?> 10 01> 20 <3 4 @078 =0 4>1C), =5 <0T ;:V=VG=>3> 7=0G5==O.

0AB5@565==O. >= A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 ;53:8< ?>@CH5==O< DC=:FVW ?5GV=:8 B0/01> =8@>:.

'5@57 ?V428I5=89 @878: H;C=>G:>2>W 0@8B= ?@>B8?>:070=> 70AB>A>2C20B8 ?0FVT=B0< V7 ?>4>265==O< V=B5@20;V2 A5@F52>W ?@>2V4=>ABV, 7>:@5<0 QTA, ?0FVT=B0< 7V 7=0G=8<8 ?>@CH5==O<8 10;0=AC 5;5:B@>;VBV2 (3V?>:0;VT<03=VT 1@048:0@4VTN B0 ?0FVT=B0< V7 D>=>28<8 E2>@>10<8 A5@FO, B0:8<8 O: 70ABV9=0 A5@F520 =54>AB0B=VABL. V4<>, I> ?>@CH5==O 10;0=AC 5;5:B@>;VBV2 (3V?>:0;VT<03=VT

28?04:C ?>O28 A8 <>6CBL 1CB8 ?>2O70=V V7 A5@F52>N 0@8BAC20==O >B8=>;C ?>B@V1=> ?@8?8=8B8, 0 ?0FVT=BC A;V4 =5309=> ?@>:>=AC;LBC20B8AO V7 ;V:0@5

>@CH5==O DC=:FVW =8@>: . 5@V>4 =0?V2282545==O 4>=C ?@8 BO6:>@CH5==V DC=:FVW =8@>: ?>4>265=89. @8 B@820;>BC 70AB>AC20==O 4>=C A;V4 7<5=H8B8 4> >4=>3> 01> 42>E @07V2 =0 4>1C 70;56=> 2V4 BO6:>ABV ?>@CH5==O. "0:>6 <>65 28=8=:CB8 ?>B@510 2 7=865==V 4>78.

=B0F84=V 01> 0=B8A5:@5B>@=V ?@5?0@0B8 =5 A;V4 ?@89<0B8 >4=>G0A=> 7 ?5@>@0;L=8<8 D>@ <0<8 ?@5?0@0BC 4>=, >A;V;L:8 2>=8 7=86CNBL ?5@>@0;L=C 1V>4>ABC?=VABL 4>C (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). @8 ACAC20==V 4>= A;V4 ?@89<0B8 ?5@54 W4>N, 0 0=B0F84=V 01> 0=B8A5:@5B>@=V ?@5?0@0B8 ?VA;O W48.

0AB>AC20==O 7 :5B>:>=07>;> # 4>A;V465==OE 270T<>4VW 7 ?5@>@0;L=>N D>@<>N :5B>:>=07>;C 2V47=0G0;>AL ?>4>265==O QT-V=B5@20;C. %>G0 7=0G5==O FL>3> O28I0 GVB:> =5 2AB0=>2;5=>, A;V4 >1@0B8 0;LB5@=0B82=5 ;V:C20==O, O:I> ?>:070=0 ?@>B83@81:>20 B5@0?VO :5B>:>=07>;> "01;5B:8 >B8=>; 7C, B>A>2C20B8 ?0FVT=B0< 7 =5?5@5=>A878, 30;0:B>75

!;V4 2@0E>2C20B8 =86G5=0254C V=D>@<0FVN AB>A>2=> @878:C @>728B:C CA:;04=5=L A5@F52>-AC48==8E 70E2>@N20=L, 7C<>2;5=8E ;V:0@AL:8<8 70A>10<8, I> =:

● 5O:V 5?V45;>3VG=V 4>A;V465==O ?>:070;8, I> 4>= ?V428ICT @878: A5@9>7=8E H;C=>G:>28E 0@8B @0?B>2>W A5@F52>W A<5@BV.

● 878: A5@9>7=8E H;C=>G:>28E 0@8B @0?B>2>W A5@F52>W A<5@BV 28I89 C ?0FVT=BV2 2V:<< 2V4

60 @>:V2 B0 C @07V ?5@>@0;L=>3> 70AB>AC20==O 4>7 ?@5?0@0BC 1V;LH5 30<3 =0 4>1C. ">
15@56=VABN 70AB>A>2C20B8 4>= ?0FVT=B0< ;VB=L>3> 2V:C. 0FVT=B0< 2V:< 2V4 60 @>:V2
?5@54 ?@89><<< 4>=C A;V4 ?@>:=AC;LBC20B8AO 7 ;V:0@5

● >= A;V4 ?@87=0G0B8 4>@>A;8< B0 4VBO< C =09=86GV9 5D5:B82=V9 4>7V.
! ?V22V4=>H5==O @878:C B0 :>@8ABV 4>=C 70;8H0TBLAO A?@8OB;828

A>1;82V 70AB5@565==O.

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

0=V I>4> ?>AB<0@:5B8=3>2>3> 70AB>AC20==O 4>=C 203VB=8<8 6V=:0<8 >1<565=V. @5?0@0B C
?5@V>4 203VB=>ABV A;V4 70AB>A>2C20B8 ?VA;O :=AC;LB0FVW 7 ;V:0@5< BV;L:8 2 B>;8
>GV:C20=89 B5@0?52B8G=89 5D5:B ?5@528ICT ?>B5=FBV9=89 @878: 4;O <0B5@V V ?;>40.
4>A;V465==OE 1C;> ?>:070=>, I> 4>= ?@>=8:0T C 3@C4=5 <>;>: 52V4><>, G8 2V= H:>48BL =5
<>2;OBV, B>4C20==V. '5@57 ?@>=8:=5==O ?@5?0@0BC C 3@C4=5 <>;>: =5 <>6=0 28;;NG8B8 ?>O2C
C 4VB59 ?>1VG=8E 5D5:BV2, 7>:@5<0 :0@4V>;>3VG=8E 5D5:BV2.

**40B=VABL ??;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.**

@0E>2CNG8 ?>1VG=C 4VN 7 1>:C =5@2>2>W A8AB5<8, ?0FVT=B0< =5>1EV4=> 1CB8 C206=8<8 ?@8
:5@C20==V 02B>B@0=A?>@B< 01> @>1>BV 7 V=H8<8 <5E0=V7<0<8.

VB8.

@5?0@0B 70AB>A>2C20B8 4;O ;V:C20==O 4VB59 2V:< 2V4 12 @>:V2 V <0A>N BV;0 =5 <5=H5 35 :3.
>= A;V4 70AB>A>2C20B8 4VBO< C =09=86GV9 5D5:B82=V9 4>7V ?@>BO3< =09:>@>BH>3>
?5@V>4C.

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

"01;5B:8 >B8=>;C ?@87=0G5=V 4;O ?5@>@0;L=>3> 70AB>AC20==O.

;O ?>;53H5==O A8B8 B0 1;N20==O.

>@>A;V V 4VB8 2V:< 2V4 12 @>:V2 V <0A>N BV;0 =5 <5=H5 35 :3: ?> 1 B01;5BFV (10 <3) 3 @078 =0
4>1C.

0:A8<0;L=0 4>1>20 4>70 3 B01;5B:8 (30 <3 =0 4>1C).

5:<5=4CTBLAO ?@89<0B8 ?@5?0@0B >B8=>; ?5@54 ?@89><<< W6V. A<>:BC20==O ?@5?0@0BC
45I> 70B@8 9>3> ?@89<0B8 ?VA;O ?@89>"@820;VABL ;V:C20==O =5 ?>28==O ?5@528IC20B8 1
B8645=L.

5@54>7C20==O.

!8<8: A8<0<8 ?5@54>7C20==O <>6CBL 1CB8 068B0FVO, ?>@CH5==O A2V4><>ABV, AC4<8,
457>@VT=B0FVO, A>=;82VABL B0 5:AB@0?V@0
V:C20==O. !?5F8DVG=>3> 0=B84>BC 4>=C =5<0T, 0;5 C 28?04:C 7=0G=>3> ?5@54>7C20==O @5:>
<5=4>20=5 ?@><820==O H;C=:0 ?@>BO3>< 1 3>48=8 ?VA;O ?@89>AC20==O 0:B82>20=>3> 2C3V;;O, 0
B0:>6 ?8;L=5 A?>AB5@565==O 70 ?0FVT=B< B0 ?V4B@8;V=5@3VG=V ?@5?0@0B8, 70A>18 4;O
;V:C20==O E2>@>18 0@:V=A>=0 <>6CBL 1CB8 5D5:B82=8<8 4;O :=B@>;N 5:AB@0?V@0

>1VG=V @50:FVW.

0 C<>28 4>B@8<0==O @5:><5=40FV9 7 4>7C20==O B0 B@820;>ABV ;V:C20==O 4>= 70728G09
?5@5=>A8BLAO 4>1@5, V =51060=V O28I0 28=8:0NBL =5G0AB>.

I>:C VW A8AB5<8: 0;5@3VG=V @50:FVW, 2;;NG0NG8 0=0DV;0:AVN, 0=0DV;0:B8G=89 H>;,
3V?5@GCB;82VABL.

I>:C 5=4>:@8==>W A8AB5<8: ?V428I5==O @V2=O ?@>;0:B8=C.

A8EVG=V @>7;048: =5@2>7=VABL, @>74@0B>20=VABL, 71C465==O, 45?@5AVO, B@82>6=VABL,
7=865==O 01> 2V4ACB=VABL ;V1V4>.

I>:C =5@2>2>W A8AB5<8: 157A>==O, 70?0<>@>G5==O, A?@030, AC4<8, <;O2VABL, 3>;>2=89 1V;L,
A>=;82VABL, 0:0B87VO, 5:AB@0?V@07;048.

I>:C A5@F52>-AC48==>W A8AB5<8: =01@O.; 2V4GCBBO A5@F518BBO, ?>@CH5==O G0AB>B8 B0 @8B@>G5=L, ?>4>265==O V=B5@20;C QT (G0AB>B0 =52V4<0), A5@9>7=V H;C=>G:>2V 0@8B G:>2V 0@8B B8?C «torsade de pointes», @0?B>20 A5@F520 A<5@BL.

I>:C H;C=:>2>-.8H:>2>3> B@0:BC: 30AB@>V=B5AB8=0;L=V @>7;048, 2.;NG0NG8 014>BC, ?5GVN, 70?>@, ACEVABL C @>BV, :>@>B:>G0A=V :8H:>2V A?078, 4V0@5O.

I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: A25@1V6, 28A8?0==O, :@>?82O=:0, 0=3V>=52@>B8G=89 =01@O:.

I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: 30;0:B>@5O, 71V;LH5==O <>;>G=8E 70;>7 /3V=5:><0ABVO, GCB;82VABL <>;>G=8E 70;>7, 284V;5==O 7 <>;>G=8E 70;>7, 0<5=>@5O, =01@O: <>;>G=8E 70;>7, 1V;L C 4V;O=FV <>;>G=8E 70;>7, ?>@CH5==O ;0:B0FVW, =5@53C;O@=89 <5=AB@C0;L=89 F8;.

I>:C >?>@=>-@CE>2>W A8AB5<8 B0 A?>;CG=>W B:0=8=8: 1V;L C =>30E.

I>:C A5G>284V;L=>W A8AB5<8: 70B@828?CA:0==O.

030;L=V @>7;048: 0AB5=VO.

I>:C >@30=V2 7>@C: >:C;>3V@=V :@878.

=H5: :>=N=:B82VB, AB<>0B8B.

@0B>@=8E ?>:07=8:V2: ?V428I5==O @V2=O 0;0=V=0B@0=AD5@078 ("), 0A?0@03V=0 B@0=AD5@078 (!") V E>;5AB5@8=C, 2V4E8;5==O 2V4 =>@<8 ?>:07=8:V2 DC=:FV>=0;L=8E B5ABV2 ?5GV=:8, ?V428I5==O @V2=O ?@>;0:B8=C C :@>2V.

A:V;L:8 3V?>DV7 7=0E>48BLAO ?>70 35<0B>5=F5D0;VG=8< 10@T@<, 4>= <>65 A?@8G8=8B8

?V428I5==O @V2=O ?@>;0:B8=C. # ?>>48=>:8E 28?04:0E B0:0 3V?5@?@>;0:B8=5

?5@V>4 ?>AB<0@:5B8=3>2>3> 70AB>AC20==O ?@5?0@0BC 2V4AB59 C ?@>DV;V 157?5:8

70AB>AC20==O ?@5?0@0BC C 4>@>A;8E B0 4VB59 2V47=0G5=>=5 1C;>, 70 28=OB:>< 5:AB@0?V@0

7;04V2 B0 V=H8E O28I, AC4<< V 71C465==O, ?>2O70=8E V7 F5=B@0;L=>N =5@2>2>N A8AB5<>N, I>

A?>AB5@V30;8AO ?5@5206=> C 4VB59.

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

=B8E>;V=5@3VG=V ?@5?0@0B8 <>6CBL =59B@0;V7C20B8 0=B848A?5?B8G=C 4VN >B8=>;C. #

72O7:C 7 D0@<0:>48=0N B0/01> D0@<0:>:V=5B8G=>N 270T<>4VO<8 ?V428ICTBLAO @878:

28=8:=5==O ?>4>265==O Q"-V=B5@20;C.

5 A;V4 ?@89<0B8 0=B0F84=V B0 0=B8A5:@5B>@=V ?@5?0@0B8 >4=>G0A=> V7 >B8=>;<, >A:V;L:8 2>=8 7=86CNBL 9>3> 1V>4>ABC?=VABL ?VA;O ?@89>(482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

>= <5B01>;V7CTBLAO ?5@5206=> 70 4>?><>3>N CYP3A4. 0 40=8<8 4>A;V465=L Vn vitro, AC?CB=T

70AB>AC20==O ?@5?0@0BV2, I> 7=0G=8< G8=>< ?@83=VGCNBL F59 D5@<5=B, <>65 ?@8725AB8 4>

?V428I5==O @V2=O 4>=C C ?;072V.

@8 70AB>AC20==V 4>=C AC?CB=L> V7 ?>BC6=8<8 V=3V1VB>@0<8 CYP3A4, 740B=8<8 ?>4>26C20B8

V=B5@20; QT, A?>AB5@V30;8AO ;;V=VG=> 7=0GCIV 7AC20==O 4>=C 7 ?52=8<8 ?@5?0@0B0<8

?@>B8?>:070=5 (482. @>74V; «@>B8?>:070==O»).

!C?CB=T 70AB>AC20==O =86G5=02545=8E ;V:0@AL:8E 70A>1V2 @07>< 7 4>=>< ?@>B8?>:070=5.

#AV;V:0@AL:V 70A>18, O:V ?>4>26CNBL V=B5@20; QT:

- 0=B80@8B (=0?@8::04, 487?>V@0EV=V48=);
- 0=B80@8B (=0?@8::04, 040@>=, 4>D5B8;V4, 4@>=540@>=, V1CB8;V4, A>B0;>);
- 45O:V =59@>;5?B8G=V ?@5?0@0B8 (=0?@8::04, 30;>?5@84>;, ?V<>784, A5@B8=4>);
- 45O:V 0=B845?@5A0=B8 (=0?@8::04, F8B0;>?@0<, 5AF8B0;>?@0<);
- 45O:V 0=B81V>B8:8 (=0?@8::04, ;52>D;>:A0F8=, <>:A8D;>:A0F8=, 5@8B@>|
- 45O:V ?@>B83@81:>2V ?@5?0@0B8 (=0?@8::04, ?5=B0|
- 45O:V ?@>B8<0;O@V9=V ?@5?0@0B8 (=0?@8::04, 30;>D0=B@8=, ;N<5D0=B@8=);
- 45O:V H;C=:>2>-.8H:>2V ?@5?0@0B8 (=0?@8::04, F870?@84, 4>;0A5B@>=, ?@C:0;>?@84);
- 45O:V 0=B83VAB0;0AB8=);
- 45O:V ?@5?0@0B8, I> 70AB>A>2CNBLAO ?@8 >=;>;>3VG=8E 70E2>@N20==OE (=0?@8::04, B>@5|
- 45O:V V=HV ?@5?0@0B8 (=0?@8::04, 15?@848;;, <5B04>=, 48D5<0=V;).

!8;L=V V=3V1VB>@8 CYP3A4, 7 O:8<8 ?@>B8?>:070=> 70AB>A>2C20B8 >B8=>;:

- 07>;L=V ?@>B83@81:>2V ?@5?0@0B8, B0:V O: D;C:=>07>;*, VB@0:=>07>;, :5B>:>=07>;* V

2>@8:>=07>;*;

- <0:@>;V4=V 0=B81V>B8:8, B0:V O: ;0@8B@>
- V=3V1VB>@8 ?@>B5078*;
- V=3V1VB>@8 -?@>B5078, B0:V O: 0A0=02V@ V A0:2V=02V@;
- 0=B03>=VAB8 :0;LFVN, B0:V O: 48;BV075< V 25@0?0
- 040@>=*;
- 0<@5?VB0=B;
- =5D07>4>=;
- B5;VB@>
*@>;>=3CNBL V=B5@20; QTc.
4=>G0A=5 70AB>AC20==O =86G52:070=8E @5G>28= 28<030T >15@56=>ABV.
15@56=> 70AB>A>2C20B8 7 ?@5?0@0B0<8, I> A?@8G8=ONBL 1@048:0@4VN V 3V?>:0;VT6 7 B0:8<8
<0:@>;V40<8, I> <>6CBL A?@8G8=8B8 ?>4>265==O V=B5@20;C QT: 078B@>.A8B@>B8?>:070=89,
>A:V;L:8 F5 ?>BC6=89 V=3V1VB>@ CYP3A4).
!;V4 7 >15@56=VABN 70AB>A>2C20B8 4>= AC?CB=L> 7 ?>BC6=8<8 V=3V1VB>@0<8 CYP3A4, O:V =5
A?@8G8=O;8 ?>4>265=L V=B5@20;C QT, B0:8<8 O: V=48=02V@, V 70 ?0FVT=B0<8 A;V4 ?8;L=>
=03;O40B8 =0 28?04>: ?>O28 A8
8I5=02545=89 ?5@5;V: T @5?@575=B0B82=8<, 0;5 =5 T 28G5@?=8
>B8=>; <>6=0 ?>T4=C20B8 7:
- =59@>;5?B8:0<8, 4VN O:8E 2V= ?>A8;NT;
- 4>D0

"5@ABV.5 @>:V2.

#<>28 715@V30==O.

15@V30B8 C =54>ABC?=>□.
5 70AB>A>2C20B8 ?VA;O 70:V=G5==O B5@ABV, 707=0G5=>3> =0 C?0:>2FV.

#?0:>2:0.

> 15 B01;5B>: C 1;VAB5@V; ?> 2 1;VAB5@8 C :0@B>==V9 :>@>1FV.

0B53>@VO 2V4?CA:C. 57 @5F5?B0.

!" #&/
> <548F8=A:>

"□□
(MOTINOL)

!>AB02 ;5:0@AB25==>3> A@54AB20:

459AB2CNI55 25I5AB2>: 4>=;
1 B01;5B:0 A>45@68B 10 <3 4>=0 2 D>@<5 4>=0 <0;50B0;
2A?><>30B5;L=K5 25I5AB20: :@0E<0; :C:C@C7=K9, =0B@8O 4>:C70B 85 % =0B@8O 15=7>0B 15
%
(211), F5;;N;>70<8:@>:@8AB0;;8G5A:0O, ;0:B>7K <>=>384@0B, ?>284>=, <03=8O AB50@0B, =0B@8O
:>A:0@<5;;>70;
A>AB02 >I>;>G:8: 38?@><5;;>70, 384@>:A8?@>?8;F5;;N;>70, B8B0=0 48>:A84 (171),
?>;8MB8;5=3;8:>;L.

5:0@AB25==0O D>@<0. "01;5B:8, ?>:@KBK5 ?;5=>G=>9 >1>;>G:>9.

"01;5B:8, ?>:@KBK5 ?;5=>G=>9 >1>;>G:>9, 15;>3> 8;8 A;53:0 :@5<>2>3> F25B0, 42>O:>2K?C::K5, :@C3;>9 D>@4=>9 AB>@>=K =0=5A5=>BB8A: ;>3>B8?0 « » 8 F8D@0 «10», A 4@C3>9 AB>@>=K B01;5B:0 3;04:00.

0720=85 8 <5AB>=0E>645=85 ?@>872>48B5;O.

\$0@<0A09=A =:., 6111 >O;<0C=B 25=N, 100, >=@50;L, 2515: 4 2"4, 0=040 / Pharmascience Inc., 6111 Royalmount Avenue 100, Montreal, Quebec H4P 2T4, Canada.

\$0@<0:>B5@0?52B8G5A:00 3@C??0. !B8@K ?5@8AB0;LB8:8. >4 " ! A03F 03.

\$0@<0:>48=0<8:0.

>= 0=B03>=8AB 4>D0<8=0 A ?@>B82>@2>B=K<8 A2>9AB20<8. >= =57=0G8B5;L=> ?@>=8:05B G5@57 35<0B>M=F5D0;8G5A:89 10@L5@. @8<5=5=85 4>=0 >G5=L @54:> A>?@>2>6405BAO M:AB@0?8@0 <84=K<8 ?>1>G=K<8 459AB28O<8, >A>15==> C 27@>A;KE, >4=0:> 4>= AB8;0:B8=0 A 38?>D870. 3> ?@>B82>@2>B=>5 459AB285, 2>7<>6=>, >1CA;>2;5=> >1J548=5=85< ?5@8D5@8G5A:>3> (30AB@>:8=5B8G5A:>3>) 459AB28O 8 0=B03>=87<0 : @5F5?B>@0< 4>D0<8=0 2 B@8335@=>9 7>=5 E5 <>@5F5?B>@>2, :>B>@K5 =0E>4OB AO 2=5 35<0B>M=F5D0;8G5A:>3> 10@L5@0 2 704=5< CG0AB:5 4>;8 (area postrema).

AA;54>20=8O =0 682>B=KE, 0 B0:65 =87:00 :>=F5=B@0F8O, :>B>@0O >?@545;O;0AL 2 <>73C, C:07K205B =0 ?@58 ?5@8D5@8G5A:>5 459AB285 4>=0 =0 @5F5?B>@K 4>D0<8=0.

AA;54>20=8O C ;N459 ?>:070;8, GB> ?@8 ?@8<5=5=88 2=CB@L 4>= ?>2KH05B 402;5=85 2 =86=8E >B45;0E ?8I52>40, C;CGH05B 0=B@>4C>45=0;L=CN <>B>@8:C 8 CA:>@O5B >?>@>6=5=85 65;C4:0. >= =5 >:07K205B 2;8O=85 =0 A5:@5F8N 65;C4:0.

\$0@<0:>:8=5B8:0.

>= E>@>H> 01A>@18@C5BAO ?@8 ?5@>@0;L=<< ?@85<5 =0B>I0:, <0:A8<0;L=0O :>=F5=B@0F8O 2 ?;07<5 4>AB8305BAO ?@81;878B5;L=> G5@57 60 <8=CB. 87:00 01A>;NB=0O 18>4>ABC?=>ABL ?5@>@0;L=>3> 4>=0 (?@81;878B5;L=> 15 %) >1CA;>2;5=0 M:AB5=A82=K< <5B01>;87<<< ?5@2>3> ?@>E>645=8O 2 AB5=:5 :8H5G=8:0 8 2 ?5G5=8. 5A<>B@O =0 B>, GB> C 74>@>2KE ;N459 18>4>ABC?=>ABL 4>=0 C25;8G8205BAO ?@8 ?@85<5 ?>A;5 54K, 1>;L=K< A 60;>10<8 65;C4>G=>- :8H5G=>3> E0@0:B5@0 A;54C5B ?@8=8<0BL 4>= 70 15-30 <8=CB 4> 54K.

!=865==0O :8A;>B=>ABL 65;C4:0 C<5=LH05B 01A>@1F8N 4>=0. @8 ?5@>@0;L=<< ?@85<5 ?@5?0@0B0 ?>A;5 54K <0:A8<0;L=0O 01A>@1F8O =5A:>;L:> 70<54;O5BAO.

@8 ?5@>@0;L=<< ?@85<5 4>= =5 0::C1AB25==K9 >1<5=. 0:A8<0;L=K9 C@>25=L 2 ?;07<5 :@>28 G5@57 90 <8=CB (21 =3/<;) ?>A;5 42CE=545;L=>3> ?5@>@0;L=>3> ?@85<0 ?> 30 <3 2 45=L 1K; B0:8< 65, :0: ?>A;5 ?@85<0 ?5@2>9 4>7K (18 =3/<;).

>= =0 91-93 % A2O7K205BAO A 15;>0<8 ?;0728. AA;54>20=8O @0A?@545;5=8O 4>=0 ?>:070;8 53> 7=0G8B5;L=>5 @0A?@545;5=85 2 B:0=OE, >4=0:>, =87:CN :>=F5=B@0F8N 2 <>73C.

>= 1KAB@> 8 M:AB5=A82=> <5B01>;878@C5BAO 2 ?5G5=8 ?CB5< 384@>:A8;8@>20=8O 8 N-450;;8;8@>20=8O.

K2545=85 A <>G>9 8 :0;<< A>AB02;O5B A>>B25BAB25==> 31 % 8 66 % >B ?5@>@0;L=>9 4>7K.

K2545=85 ?@5?0@0B0 2 =587<5=5==>< 2845 A>AB02;O5B =51>;LH>9 ?@>F5=B (10 % A :0;<< 8

?@81;878B5;L=> 1 % - A <>G>9). 5@8>4 ?>;C2K2545=8O 87 ?;07A;5 ?@85<0 @07>2>9 4>7K

A>AB02;O5B 7-9 G0A>2 C 74>@>2KE 4>1@>2>;LF52, => C 1>;L=KE A BO65;>9 ?>G5G=>9

=54>AB0B>G=>ABL N => 1>;55 4;8B5;L=K9.

>:070=8O : ?@8<5=5=8N.

;O >1;53G5=8O A8<>2 B>H=>BK 8 @2>BK.

@>B82>?>:070=8O.

>B8=>; ?@>B82>?>:070=:

- 1>;L=K< A ?>2KH5==>9 GC2AB28B5;L=>ABL N : ?@5?0@0BC 8;8 2A?<>30B5;L=K< 25I5AB20<;

- 1>;L=K< A ?@>;0:B8=-A5:@5B>@=>9 >?CE>;LN 38?>D870 (?@>;0:B8=<<<9);

- 1>;L=K< A BO65;K<8 8;8 C<5@5==K<8 =0@CH5=8O<8 DC=:F88 ?5G5=8 8/8;8 ?>G5: (A15==>AB8 ?@8 <5=5=8O»);

- 1>;L=K< A C4;8=5=85< 8=B5@20;>2 A5@45G=>9 ?@>2>48<>AB8, 2 G0AB=>AB8 QTc, 1>;L=K< A>7=0G8B5;L=K<8 =0@CH5=8O<8 10;0=A0 M;5:B@>;8B>2 8;8 A D=>=2K<8 701>;520=8O<8 A5@4F0, B0:8<8 :0: 70AB>9=0O A5@45G=0O =54>AB0B>G=>ABL (A15=>AB8 ?@8<5=5=8O»);
- 1>;L=K< A ?5G5=>G=>9 =54>AB0B>G=>ABLN;
- 5A;8 AB89 DC=:F88 65;C4:0 <>65B 1KBL >?0A=>9, =0?@8<5@ ?@8 65;C4>G=>.:8H5G=><<:@>2>B5G5=88, <5E0=8G5A:>9 =5?@>E>48<>AB8 8;8 ?5@D>@0F88;
- ?@8 >4=>2@5<5=>< ?@8<5=5=88 :5B>:>=07>;0, M@8B@><8F8=0 8;8 4@C38E A8;L=>459AB2CNI8E 8=3818B>@>2 CYP3A4;
- ?@8 >4=>2@5<5=>< ?@8<5=5=88 ;5:0@AB25==KE A@54AB2, :>B>@K5 C4;8=ONB 8=B5@20; QT, B0:8E :0: D;C:>=07>;, M@8B@><8F8=, 8B@0:>=07>;, ?5@>@0;L=K9 :5B>:>=07>;, ?>A0:>=07>;, @8B>=028@, A0:28=028@, B5;0?@528@, 2>@8:>=07>;, ;:0@8B@><8F8=, 0<8>40@>=, B5;8B@><8F8=(A15=>AB8 ?@8<5=5=8O» 8 «708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289»).

A>15=>AB8 ?@8<5=5=8O.

>= =5 @5:><5=4C5BAO ?@8 C:0G820=88.

>= A;54C5B ?@8<5=OBL A >AB>@>6=>ABLN ?0F85=B0< ?>68;>3> 2>7@0AB0 8 ?0F85=B0< A 8<5NI8 ;520=85< A5@4F0 8;8 A 701>;520=85< A5@4F0 2 0=0<=575.

!5@45G=>-A>AC48ABK5 MDD5:BK. >= 1K; A2O70= A ?@>;>=30F859 8=B5@20;0 QT =0 -. > 2@5AB <0@:5B8=3>2>3> =01;N45=8O 70D8:A8@>20=K >G5=L @54:85 A;CG08 ?@>;>=30F88 QT 8 B@5?5B0=8O<5@F0=8O 65;C4>G:>2 C ?0F85=B>2, ?@8=8<02H8E 4>=. -B8 ?0F85=BK 8<5;8 B0:65 4@C385 D0:B>@K @8A:0, M;5:B@>;8B=K5 =0@CH5=8O 8;8 ?@>E>48;8 A>?CBAB2CNICN B5@0?8N. !>3;0A=> @5:><5=40F8O< ICH-14, 1K;> ?@>2545=> 8AA;54>20=85 A B10B5;L=K< 87CG5=85< 8=B5@20;0 QT C 74>@>2KE ;8F. #4;8=5=85 8=B5@20;0 QT, :>B>@>5 =01;N40;8 2 8AA;54>20=88 ?@8 ?@8<5=5=88 4>=0 2 >1KG=KE B5@0?52B8G5A:8E 4>70E (?> 10 8;8 20 <3 4 @070 2 ACB:8), =5 8<55B ;:8=8G5A:>3> 7=0G5=8O.

@54>AB5@565=8O. >= A;54C5B A >AB>@>6=>ABLN ?@8<5=OBL ?0F85=B0< A ;53:8< =0@CH5=85< DC=:F88 ?5G5=8 8/8;8 ?>G5:.

7-70 ?>2KH5=>3> @8A:0 65;C4>G:>2>9 0@8B<88 4>= ?@>B82?>:070=> ?@8<5=OBL ?0F85=B0< A C4;8=5=85< 8=B5@20;>2 A5@45G=>9 ?@>2>48<>AB8, 2 G0AB=>AB8 QTA, ?0F85=B0< A>7=0G8B5;L=K<8 =0@CH5=8O<8 10;0=A0 M;5:B@>;8B>2 (38?>:0;85<859, 38?5@:0;85<859, 38?><03=85 <859) 8;8 1@048:0@4859 8 ?0F85=B0< A D=>=2K<8 701>;520=8O<8 A5@4F0, B0:8<8 :0: 70AB>9=0O A5@45G=0O =54>AB0B>G=>ABL. 725AB=>, GB> =0@CH5=85 10;0=A0 M;5:B@>;8B>2 (38?>:0;85<8O, 38?5@:0;85<8O, 38?><03=85<8O) 8 1@048:0@48O O2;ONBAO A>AB>O=8O<8, ?>2KH0NI8<8 ?@>0@8B <>35==K9 @8A:.

A;CG05 ?>O2;5=8O A8<>2, :>B>@K5 <>3CB 1KBL A2O70=K A A5@45G=>9 0@8B<859, ?@8<5=5=85 >B8=>;0 =C6=> ?@5:@0B8BL, 0 ?0F85=BC A;54C5B =5<54;5=> ?@>:>=AC;LB8@>20BLAO A 2@0G> 0@CH5=85 DC=:F88 ?>G5:. 5@8>4 ?>;C2K2545=8O 4>=0 ?@8 BO65;>< =0@CH5=88 DC=:F88 ?>G5: C4;8=5=. @8 4;8B5;L=>< ;5G5=88 G0AB>BC ?@8<5=5=8O 4>=0 A;54C5B C<5=LH8BL 4> >4=>3> 8;8 42CE @07 2 ACB:8 2 7028A8<>AB8 >B BO65AB8 =0@CH5=8O. "0:65 <>65B ?>B@51>20BLAO A=865=85 4>7K.

=B0F84=K5 8;8 0=B8A5:@5B>@=K5 ?@5?0@0BK =5 A;54C5B ?@8=8<0BL >4=>2@5<5=> A ?5@>@0;L=K<8 D>@<0<8 ?@5?0@0B0 4>=, ?>A:>;L:C >=8 A=860NB ?5@>@0;L=CN 18>4>ABC?=>ABL 4>=0 (A

@8<5=5=85 A :5B>:>=07>;><. 8AA;54>20=8OE 2708<>459AB28O A ?5@>@0;L=>9 D>@<>9 :5B>:>=07>;0 >B<5G0;>AL C4;8=5=85 QT-8=B5@20;0. %>BO 7=0G5=85 MB>3> O2;5=8O G5B:> =5 CAB0=>2;5=>, A;54C5B 2K1@0BL 0;LB5@=0B82=>5 ;5G5=85, 5A;8 ?>:070=0 ?@>B82>3@81:>20O B5@0?8O :5B>:>=07>;>

"01;5B:8 >B8=>; A>45@60B ;0:B>7C, ?>MB>

!;54C5B CG8BK20BL A;54CNICN 8=D>@<0F8N >B=>A8B5;L=> @8A:0 @0728B8O >A;>6=5=89 A5@45G=>-A>AC48ABKE 701>;520=89, >1CA;>2;5==KE ;5:0@AB25==K<8 A@54AB20<8, A>45@60I8 <8 4>=:

● 5:>B>@K5 M?845<8>;>38G5A:85 8AA;54>20=8O ?>:070;8, GB> 4>= ?>2KH05B @8A: A5@L57=KE 65;C4>G:>2KE 0@8B<89 8;8 2=570?=>9 A5@45G=>9 A<5@B8.

● 8A: A5@L57=KE 65;C4>G:>2KE 0@8B<89 8;8 2=570?=>9 A5@45G=>9 A<5@B8 2KH5 C ?0F85=B>2 AB0@H5 60 ;5B 8 2 A;CG05 ?5@>@0;L=>3> ?@8<5=5=8O 4>7 ?@5?0@0B0 1>;55 30 <3 2 ACB:8. >MB> AB>@>6=>ABLN ?@8<5=OBL 4>= ?0F85=B0< ?>68;>3> 2>7@0AB0. 0F85=B0< 2 2>7@0AB5 >B 60 ;5B ?5@54 ?@85<>< 4>=0 A;54C5B ?@>:=AC;LB8@>20BLAO A 2@0G>
● => A;54C5B =07=0G0BL 27@>A;K< 8 45BO< 2 A0<>9 =87:>9 MDD5:B82=>9 4>75.
!>>B=>H5=85 @8A:0 8 ?>;L7K 4>=0 >AB05BAO 1;03?>@8OB=K

A>1K5 ?@54>AB5@565=8O.

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

0==K5 ?>AB<0@:5B8=3>2>3> ?@8<5=5=8O 4>=0 15@5<5==K< 65=I8=0< >3@0=8G5==K5. @5?0@0B 2 ?5@8>4 15@5<5==>AB8 A;54C5B ?@8<5=OBL ?>A;5 :=AC;LB0F88 A 2@0G< B>;L:> 2 B<< A;CG05, :>340 >68405B5=F80;L=K9 @8A: 4;O <0B5@8 8 ?>;>40.
8AA;54>20=8OE 1K;> ?>:070=>, GB> 4>= ?@>=8:05B 2 3@C4=>5 <>;>.: 58725AB=>, >:07K205B ;8 >= 2@54 <;045=FC, ?>MB>

!>>A>1=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A 4@C38<8 <5E0=87<0<8.

#G8BK200 ?>1>G=>5 459AB285 A> AB>@>=K =5@2=>9 A8AB5

5B8.

@5?0@0B ?@8<5=OBL 4;O ;5G5=8O 45B59 2 2>7@0AB5 >B 12 ;5B 8 A<0AA>9 B5;0 =5 <5=55 35 :3.
>= A;54C5B ?@8<5=OBL 45BO< 2 A0<>9 =87:>9 MDD5:B82=>9 4>75 2 B5G5=85 :>@>B:>3> ?5@8>40.

!>>A>1 ?@8<5=5=8O 8 4>7K.

"01;5B:8 >B8=>;0 ?@54=07=0G5=K 4;O ?5@>@0;L=>3> ?@8<5=5=8O.

;O >1;53G5=8O A8<>2 B>H=>BK 8 @2>BK.

7@>A;K5 8 45B8 AB0@H5 12 ;5B 8 A<0AA>9 B5;0 =5 <5=55 35 :3: ?> 1 B01;5B:5 (10 <3) 3 @070 2 ACB:8.
0:A8<0;L=0O ACB>G=0O 4>70 3 B01;5B:8 (30 <3 2 ACB:8).

5:><5=4C5BAO ?@8=8<OBL ?@5?0@0B >B8=>; ?5@54 ?@85<>< ?8I8. A0AK20=85 ?@5?0@0B0 =5A:>;L:> 7045@68205BAO, 5A;8 53> ?@8=8<OBL ?>A;5 ?@85<0 ?8I8. @>4>;68B5;L=>ABL ;5G5=8O =5 4>;6=0 ?@52KH0BL 1 =545;N.

5@54>78@>2:0.

!8: A8<0<8 ?5@54>78@>2:8 <>3CB 1KBL 068B0F8O, =0@CH5=85 A>7=0=8O, AC4>@>38,

457>@85=B0F8O, A>=;82>ABL 8 M:AB@0?8@0<84=K5 @50:F88.

5G5=85. !?5F8D8G5A:>3> 0=B84>B0 4>=0 =5B, => 2 A;CG05 7=0G8B5;L=>9 ?5@54>78@>2:8 @5:> <5=4>20=> ?@>A;5 ?@85<0 ?@5?0@0B0 8 ?@8<5=5=85 0:B828@>20==>3> C3;O, 0 B0:65 BI0B5;L=>5 =01;N45=85 70 ?0F85=B<< 8 ?>445@6820NI0O B5@0?8O. =B8E>;8=5@38G5A:85 ?@5?0@0BK, A@54AB20 4;O ;5G5=8O 1>;57=8 0@:8=A>=0 <>3CB 1KBL MDD5:B82=K<8 4;O :=B@>;O M:AB@0?8@0<84=KE @50:F89.

>1>G=K5 @50:F88.

@8 CA;>288 A>1;N45=8O @5:><5=40F89 ?> 4>78@>2:5 8 ?@>4>;68B5;L=>AB8 ;5G5=8O 4>= >1KG=> E>@>H> ?5@5=>A8BAO, 8 =565;0B5;L=K5 O2;5=8O 2>7=8:0NB =5G0AB>.

!> AB>@>=K 8<9 A8AB5: 0;;5@38G5A:85 @50:F88, 2;;NG0O 0=0D8;0:A8N, 0=0D8;0:B8G5A:89 H>;, 38?5@GC2AB28B5;L=>ABL.

!> AB>@>=K M=4>:@8==>9 A8AB5: ?>2KH5=85 C@>2=O ?@>;0:B8=0.

A8E8G5A:85 @0AAB@>9AB20: =5@2>7=>ABL, @074@068B5;L=>ABL, 2>71C645=85, 45?@5AA8O, B@52>6=>ABL, A=865=85 8;8 >BACBAB285 ;8184>.

!> AB>@>=K =5@2=>9 A8AB5: 15AA==8F0, 3>;>2>:@C65=85, 60640, AC4>@>38, 2O;>ABL, 3>;>2=0O 1>;L, A>=;82>ABL, 0:0B878O, M:AB@0?8@0<84=K5 @0AAB@>9AB20.

!> AB>@>=K A5@45G=>-A>AC48AB>9 A8AB5: >B5.; >ICI5=85 A5@4F5185=8O, =0@CH5=85 G0AB>BK 8 @8B<0 A5@45G=KE A>:@0I5=89, C4;8=5=85 8=B5@20;0 QT (G0AB>B0 =58725AB=0), A5@L57=K5 65;C4>G:>2K5 0@8B<88, 65;C4>G:>2K5 0@8B<88 ?> B8?C «torsade de pointes», 2=570?=0O A5@45G=0O A<5@BL.

!> AB>@>=K 65;C4>G=>-.8H5G=>3> B@0:B0: 30AB@>8=B5AB8=0;L=K5 @0AAB@>9AB20, 2;:NG00
014><8=0;L=CN 1>;L, @53C@38B0F8N, 87<5=5=85 0??5B8B0, B>H=>BC, 876>3C, 70?>@, ACE>ABL 2>
>@BC, :@0B:>2@5<5==K5 :8H5G=K5 A?07

!> AB>@>=K :>68 8 ?>4:>6=KE B:0=59: 7C4, AK?L, :@0?82=8F0, 0=38>=52@>B8G5A:89 >B5:.

!> AB>@>=K @5?@>4C:B82=>9 A8AB5: 30;0:B>@5O, C25;8G5=85 <>;>G=KE 65;57/38=5:<0AB8O,
GC2AB28B5;L=>ABL <>;>G=KE 65;57, 2K45;5=8O 87 <>;>G=KE 65;57, 0<5=>@5O, >B5: <>;>G=KE
65;57, 1>;L 2 >1;0AB8 <>;>G=KE 65;57, =0@CH5=85 ;0:B0F88, =5@53C;O@>K9 <5=AB@C0;L=K9 F8;:.

!> AB>@>=K >?>@=>-42830B5;L=>9 A8AB5548=8B5;L=>9 B:0=8: 1>;L 2 =>30E.

!> AB>@>=K <>G52K45;8B5;L=>9 A8AB5: 7045@6:0 <>G8, 487C@8O, G0AB>5 <>G58A?CA:0=85.
I185 =0@CH5=8O: 0AB5=8O.

!> AB>@>=K >@30=>2 7@5=8O: >:C;>38@=K5 :@87K.

@>G55: :=JN=:B828B, AB><0B8B.

7<5=5=8O ;01>@0B>@=KE ?>:070B5;59: ?>2KH5=85 C@>2=O 0;0=8B0<8=>B@0=AD5@07K ("),
0A?0@038=0<8=>B@0=AD5@07K (!") 8 E>;5AB5@8=0, >B:;>=5=85 >B =>@:070B5;59 DC=:F8>=0;L=KE
B5AB>2 ?5G5=8, ?>2KH5=85 C@>2=O ?@>;0:B8=0 2 :@>28.

>A:>;L:C 38?>D87 =0E>48BAO 2=5 35<0B>M=F5D0;8G5A:>3> 10@L5@0, 4>= <>65B ?@825AB8 :
>?2KH5=8N C@>2=O ?@>;0:B8=0. @54:8E A;CG0OE B0:0O 38?5@?@>;0:B8=5<8O <>65B ?@82>48BL :
=59@>M=4>:@8==K< ?>1>G=K< MDD5:B0<, B0:8< :0: 30;0:B>@5O, 38=5:<0AB8O 8 0<5=>@5O.
?5@8>4 ?>AB<0@:5B8=3>2>3> ?@8<5=5=8O ?@5?0@0B0 @07;8G89 2 ?@>D8;5 157?>0A=>AB8 ?@8
<5=5=8O ?@5?0@0B0 C 27@>A;KE 8 45B59 >B<5G5=> =5 1K;>, 70 8A:;NG5=85< M:AB@0?8@0<84=KE
@0AAB@>9AB2 8 4@C38E O2;5=89, AC4>@>3 8 2>71C645=8O, A2O70==KE A F5=B@0;L=>9 =5@2=>9
A8AB5<>9, :>B>@K5 =01;N40;8AL ?@58 C 45B59.

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

=B8E>;8=5@38G5A:85 ?@5?0@0BK <>3CB =59B@0;87>20BL 0=B848A?5?B8G5A:>5 459AB285 >B8=>;0.
A2O78 A D0@<0:>48=0<8G5A:8< 8/8;8 D0@<0:>:8=5B8G5A:8< 2708<>459AB285< ?>2KH05BAO @8A:
2>7=8:=>25=8O C4;8=5=8O Q"-8=B5@20;0.

5 A;54C5B ?@8=8<0BL 0=B0F84=K5 8 0=B8A5:@5B>@=K5 ?@5?0@0BK >4=>2@5<5==> A >B8=>;<,
>?A:>;L:C >=8 A=860NB 53> 18>4>ABC?=>ABL ?>A;5 ?@85<0 2=CB@L (A15==>AB8 ?@8<5=5=8O)).
>= <5B01>;878@C5BAO ?@58 A ?>>ILN CYP3A4. > 40==K< 8AA;54>20=89 Vn vitro, >4=>2@5<5==>5
?@8<5=5=85 ?@5?0@0B>2, :>B>@K5 2 7=0G8B5;L=>9 AB5?5=8 ?>402;ONB MB>B D5@<5=B, <>65B
?@825AB8 : ?>2KH5=8N C@>2=O 4>=0 2 ?;07<5 :@>28.

@8 ?@8<5=5=88 4>=0 >4=>2@5<5==> A <>I=K<8 8=3818B>@0<8 CYP3A4, A?>A>1=K<8 C4;8=OBL
8=B5@20; QT, =01;N40;8AL ;:8=8G5A:8 7=0G84=>2@5<5==>5 ?@8<5=5=85 4>=0 A >?@545;5==K<8
?@5?0@0B0<8 ?@>B82>?>:070=> (AB82>?>:070=8O)).

4=>2@5<5==>5 ?@8<5=5=85 A;54CNI8E ;5:0@AB25==KE A@54AB2 2<5AB5 A 4>=><
?@>B82>?>:070=>.

A5 ;5:0@AB25==K5 A@54AB20, :>B>@K5 C4;8=ONB 8=B5@20; QT:

- 0=B80@8B<8G5A:85 ?@5?0@0BK ;:0AA0 I(=0?@8<5@, 487?>8@0<84, E8=848=, 384@>E8=848=);
 - 0=B80@8B<8G5A:85 ?@5?0@0BK ;:0AA0 III (=0?@8<5@, 0<8>40@>=, 4>D5B8;84, 4@>=540@>=, 81CB8;84, A>B0;>);
 - =5:>B>@K5 =59@>;5?B8G5A:85 ?@5?0@0BK (=0?@8<5@, 30;>?5@84>;, ?8<>784, A5@B8=4>);
 - =5:>B>@K5 0=B845?@5AA0=BK (=0?@8<5@, F8B0;>?@0<, MAF8B0;>?@0<);
 - =5:>B>@K5 0=B818>B8:8 (=0?@8<5@, ;52>D;>:A0F8=, <>:A8D;>:A0F8=, M@8B@><8F8=, A?8@0<8F8=);
 - =5:>B>@K5 ?@>B82>3@81:>2K5 ?@5?0@0BK (=0?@8<5@, ?5=B0<848=);
 - =5:>B>@K5 ?@>B82><0;O@89=K5 ?@5?0@0BK (=0?@8<5@, 30;>D0=B@8=, ;N<5D0=B@8=);
 - =5:>B>@K5 65;C4>G=>-.8H5G=K5 ?@5?0@0BK (=0?@8<5@, F870?@84, 4>;0A5B@>=, ?@C:0;>?@84);
 - =5:>B>@K5 0=B838AB0<8==K5 ?@5?0@0BK (=0?@8<5@, <5:8B078=, <87>;0AB8=);
 - =5:>B>@K5 ?@5?0@0BK, ?@8<5=O5=:;>38G5A:8E 701>;520=8OE (=0?@8<5@, B>@5<8D5=, 20=45B0=81, 28=:0<8=);
 - =5:>B>@K5 4@C385 ?@5?0@0BK (=0?@8<5@, 15?@848;, <5B04>=, 48D5<0=8);
- 18;L=K5 8=3818B>@K CYP3A4, A :>B>@K<8 ?@>B82>?>:070=> ?@8<5=OBL >B8=>;:

- 07>;L=K5 ?@>B82>3@81:>2K5 ?@5?0@0BK, B0:85 :0: D;C:>=07>;*, 8B@0:>=07>;, :5B>:>=07>;* 8
2>@8:>=07>;*;
- <0:@>;84=K5 0=B818>B8:8, B0:85 :0: ;;0@8B@><8F8=* 8 M@8B@><8F8=*;
- 8=3818B>@K ?@>B507K*;
- 8=3818B>@K '?@>B507K, B0:85 :0: 0A0=028@ 8 A0:28=028@;
- 0=B03>=8ABK :0;LF8O, B0:85 :0: 48;B8075< 8 25@0?0<8;;
- 0<8>40@>=*;
- 0<@5?8B0=B;
- =5D07>4>=;
- B5;8B@><8F8=*.
* @>;>=38@CNB 8=B5@20; QTc.

4=>2@5<5==>5 ?@8<5=5=85 A;54CNI8E 25I5AB2 B@51C5B >AB>@>6=>AB8.
AB>@>6=> ?@8<5=OBL A ?@5?0@0B0<8, 2K7K20NI8<8 1@048:0@48N 8 38?>:0;85<8N, 0 B0:65 A>
A;54CNI8<8 <0:@>;840<8, :>B>@K5 <>3CB 2K720BL C4;8=5=85 8=B5@20;0 QT: 078B@><8F8= 8
@>:A8B@><8F8= (:;0@8B@><8F8= ?@>B82>?>:070=, ?>A:>;L:C MB> <>I=K9 8=3818B>@ CYP3A4).
!;54C5B A >AB>@>6=>ABLN ?@8<5=OBL 4>=>4=>2@5<5==> A <>I=K<8 8=3818B>@0<8 CYP3A4,
:>B>@K5 =5 2K7K20;8 C4;8=5=8O 8=B5@20;0 QT, B0:8<8 :0: 8=48=028@, 8 70 ?0F85=B0<8 A;54C5B 2=8
<0B5;L=> =01;N40BL =0 A;CG09 ?>O2;5=8O A8<>2 =565;0B5;L=KE @50:F89.
KH5?@82545==K9 ?5@5G5=L O2;O5BAO @5?@575=B0B82=K<, => =5 O2;O5BAO 8AG5@?K20NI8
>B8=>; <>6=> A>G5B0BL A:
- =59@>;5?B8:0<8, 459AB285 :>B>@KE >= CA8;8205B;
- 4>D0<8=5@38G5A:8<8 03>=8AB0<8 (1@><>:@8?B8=><, L-4>?>9), =565;0B5;L=>5 ?5@8D5@8G5A:>5
459AB285 :>B>@KE, =0?@8<5@ =0@CH5=85 ?8I520@5=8O, B>H=>BC, @2>BC, >= ?>402;O5B 157
=59B@0;870F88 >A=>2=KE A2>9AB2.

!@>: 3>4=>AB8. 5 ;5B.

#A;>28O E@0=5=8O.

%@0=8BL 2 =54>ABC?=>< 4;O 45B59 <5AB5 ?@8 B5□.
5 ?@8<5=OBL ?>A;5 >:>=G0=8O A@>:0 3>4=>AB8, C:070==>3> =0 C?0:>2:5.

#?0:>2:0.

> 15 B01;5B>: 2 1;8AB5@5; ?> 2 1;8AB5@0 2 :0@B>==>9 :>@>1:5.

0B53>@8O >B?CA:0. 57 @5F5?B0.