

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

® .!
(LOZAP® PLUS)

!,:04:
4VNGV @5G>28=8: ;>70@B0= :0;VN, 3V4@>E;>@>BV0784;
1 B01;5B:0 70@B0=C :0;VN 50 <3, 3V4@>E;>@>BV0784C 12,5 <3;
4>?>28=8: <0=VB (421), F5;N;>70 :@8AB0;VG=0, =0B@VN :@>A:0@<5;>70, ?>2V4>=, <03=VN
AB50@0B, 3V?@><5;>70, <0:@>3>; 6000, B0;L:, 5B8B0=C 4V>:A84 (171), EV=>;V=>289 6>2B89 (104),
>=A> 4R (124).

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

\$0@<0;>B5@0?52B8G=0 3@C?0. ><1V=>20=V ?@5?0@0B8 V=3V1VB>@V2 0=3V>B5=78=C .
=B03>=VAB8 0=3V>B5=78=C V 4VC@5B8:8. >4 " ! CO9D A01.

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

>:070==O.

@B5@V0;L=0 3V?5@B5=7VO C ?0FVT=BV2, C O:8E <=>B5@0?VO ;>70@B0=>< 01>
3V4@>E;>@>BV0784>< =5 4>72>;OT 045:20B=> :>=B@>;N20B8 0@B5@V0;L=89 B8A:.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> ;>70@B0=C 01> 4> 1C4L-O:8E :>5=BV2 ?@5?0@0BC.

V428I5=0 GCB;82VABL 4> ?>EV4=8E AC;LD0=V;E;>@>BV0784).

578AB5=B=V 4> B5@0?VW 3V?>:0;VT 3V?5@:0;LFVT

=C@VO.

06:5 ?>@CH5==O DC=:FVW ?5GV=:8: E>;5AB07 B0 @>7;048, ?>2070=V 7 =5?@>EV4=VABN 6>2G=8E
H;OEV2.

5D@0:B5@=0 3V?>=0B@VT

!8<0B8G=0 3V?5@C@8:5403@0.

"O6:5 ?>@CH5==O DC=:FVW =8@>: (:;V@5=A :@50B8=V=C <30 <;E28;8=C).

03VB=V 01> 6V=:8, O:V ?;0=CNBL 70203VB=VB8 (482. @>74V; «0AB>AC20==O C ?5@V>4
203VB=>ABV 01> 3>4C20==O 3@C44N»).

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

>70?® ;NA <6=0 70AB>A>2C20B8 =570;56=> 2V4 ?@89>2B0B8 FV;>N, 70?820NG8 2>4>N.

>70?® ;NA <6=0 ?@87=0G0B8 AC 7 V=H8<8 0=B83V?5@B5=782=8<8 ?@5?0@0B0<8.

@B5@V0;L=0 3V?5@B5=7VO

><1V=0FVO ;>70@B0=C B0 3V4@>E;>@>BV0784C =5 ?@87=0G5=0 4;O 70AB>AC20==O C O:>ABV

?>G0B:>2>W B5@0?VW. >=0 ?>:070=0 BV;L:8 ?0FVT=B0<, C O:8E 0@B5@V0;L=89 B8A: =5 240TBLAO

045:20B=> :>=B@>;N20B8 70 4>?><3>N <=>B5@0?VW ;>70@B0=>< :0;VN 01> <=>B5@0?VW

3V4@>E;>@>BV0784><5=4CTBLAO 74V9A=8B8 B8B@C20==O 4>78 4;O :>6=>3> :>=5=B0 >:@5<> (4;O

;>70@B0=C B0 3V4@>E;>@>BV0784C). 28G09=0 ?>G0B:>20 V ?V4B@870 1 B01;5B:0 1 @07 =0 4>1C. ;O

?0FVT=BV2 157 045:20B=>W B5@0?52B8G=>W 2V4?>2V4V 4>70 ?@5?0@0BC <>65 1CB8

71V;LH5=0 4>

2 B01;5B>: 1 @07 =0 4>1C.

0:A8<0;L=0 4>70 2 B01;5B:8 1 @07 =0 4>1C. /: ?@028;>, AB01V;L=89 0=B83V?5@B5=782=89 5D5:B

4>AO30TBLAO ?@>BO3>< 3-4 B86=V2 2V4 ?>G0B:C ;V:C20==O.

0AB>AC20==O ?0FVT=B0< 7 ?>@CH5==O< DC=:FVW =8@>: B0 ?0FVT=B0<, O:V ?5@51C20NBL =0
35<>4V0;V7V

?0FVT=BV2 7 ?> ?>@CH5==O< DC=:FVW =8@>: (B>1B> :>;8 ;;V@5=A :@50B8=V=C AB0=>28BL

30-50 < ;/E28;8=C) :>@5:FVO ?>G0B:>2>W 4>78 =5 ?>B@V1=0. 5 @5:><5=4CTBLAO 70AB>A>2C20B8
B01;5B:8, O:V 70@B0= B0 3V4@>E;>@>BV0784, ?0FVT=B0<, O:V ?5@51C20NBL =0 35<>4V0;V7V. 5
A;V4 70AB>A>2C20B8 □>70?® ;NA ?0FVT=B0< 7 206:8< ?>@CH5==O< DC=:FVW =8@>: (B>1B> :>;8
::V@5=A :@50B8=V=C <30 < ;/E28;8=C) (482. @>74V; «@>B8?>:070==O»).

0AB>AC20==O ?0FVT=B0< V7 2=CB@VH=L>AC48==>N 3V?>2>;5

5@54 B8< O: 70AB>A>2C20B8 □>70?® ;NA, =5>1EV4=> A?>G0B:C 2V4:>@83C20B8
2=CB@VH=L>AC48==C 3V?>2>;5 3V?>=0B@VT

0AB>AC20==O ?0FVT=B0< 7 ?>@CH5==O< DC=:FVW ?5GV=:8

>70?® ;NA ?@>B8?>:070=89 ?0FVT=B0< 7 B06:8< ?>@CH5==O< DC=:FVW ?5GV=:8 (482. @>74V;
«@>B8?>:070==O»).

0AB>AC20==O ?0FVT=B0< ;VB=L>3> 2V:C

@8 70AB>AC20==V C ;VB=VE ?0FVT=BV2 :>@5:FVO 4>78 =5 ?>B@V1=0.

0AB>AC20==O 4VBO<

>A2V4 70AB>AC20==O ?@5?0@0BC 4VBO< 2V4ACB=V9, B>A>2C20B8 4;O ;V:C20==O 4VB59.

>1VG=V @50:FVW.

>1VG=V @50:FVW >1<56C20;8AO B0:8<8, ?@> O:V ?>2V4<;O;>AO @0=VH5 ?@8 70AB>AC20==V
;>70@B0=C B0/01> 3V4@>E;>@>BV0784C >:@5<.

0?0<>@>G5==O 1C;> T48=>N, ?>2O70=>N V7 ?@89><< ?@5?0@0BC ?>1VG=>N @50:FVTN, G0AB>B0
O:>W ?5@528IC20;0 B0:C ?@8 ?@89> 1V;LH5, O: =0 >48= 2V4A>B>:.

?@>F5AV ?>AB<0@:5B8=3>2>3> 70AB>AC20==O ?@5?0@0BC ?>2V4<;O;>AO ?@> B0:V ?>1VG=V
@50:FVW =0 ;>70@B0= :0;VN/3V4@>E;>@>BV0784.

I>:C 35?0B>1V;V0@=>W A8AB5<8: 35?0B8B

57C;LB0B8 4>A;V465=L: 3V?5@:0;VTB@0=AD5@078 (").

>40B:>2V ?>1VG=V @50:FVW, O:V A?>AB5@V30;8AO ?@8 70AB>AC20==V >4=VTW G8 4@C3>W 7
4VNG8E @5G>28= >:@5< B0 O:V ?>B5=FV9=> <>6CBL 28=8:0B8 ?@8 70AB>AC20==V :<1V=0FVW
;>70@B0=C/3V4@>E;>@>BV0784C, 2;;NG0NBL:

>1VG=V @50:FVW, ?>2O70=V 7 ;>70@B0=<

I>:C :@>2V B0 ;VW A8AB5<8: 0=5

I>:C VW A8AB5<8: =01@O:8; @50:FVW 3V?5@GCB;82>ABV (2;;NG0NG8 0=0DV;0:B8G=V @50:FVW,
0=3V>=52@>B8G=89 =01@O:, =01@O: 3>@B0=V B0 3>;>A>2>W IV;8=8, I> ?@872>48BL 4>

>1AB@C:FVW 48E0;L=8E H;OE2V B0/01> =01@O:8 >1;8GGO, 3C1, 3>B:8 V/01> O78:0); :@>?82O=:0.

@> 0=3V>=52@>B8G=89 =01@O: ?>2V4<;O;>AO C <8=C;>AC20==O< V=H8E ;V:0@AL:8E 70A>1V2, C
B>@V2 \$.

5B0I>;VG=V B0 0;V<5=B0@=V @>7;048: 0=>@5:AVO, ?>403@0.

I>:C ?A8EV:8: 157A>==O, B@82>6=VABL, B@82>6=89 =52@>7, ?0=VG=89 A8=4@<, A?;CB0=VABL

A2V4><>ABV, 45?@5AVO, =5728G09=V A=>284V==O, ?>@CH5==O A=C, A>=:82VABL, ?>@CH5==O ?0
<□OBV.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O, A;01:VABL, =5@2>7=VABL,

?0@5AB57VO, ?5@8D5@8G=0 =59@>?0BVO, B@5<>@, ?5.

I>:C >@30=V2 7>@C: =5GVB:VABL 7>@C, 2V4GCBBO ?5GV==O 01> ?>:;>N20==O 2 >G0E,

:>=N=:B82VB, 7=865==O 3>AB@>B8 7>@C.

I>:C >@30=V2 A;CEC B0 @V2=>2038: 25@B83>, 2V4GCBBO HC=C C 2CE0E.

I>:C A5@FO: 0@B5@V0;L=0 3V?>B5=7VO, >@B>AB0B8G=0 0@B5@V0;L=0 3V?>B5=7VO,
AB5@=0;3VO, AB5=>:0@4VO, 0B@V>25=B@8:C;O@=0 1;>:040 II ABC?5=O, F5@51@>20A:C;O@=V

@>7;048, V=D0@:B :0@40, ?>A8;5=5 A5@F518BBO, 0@8B20 1@048:0@4VO, B0EV:0@4VO,

H;C=>G:>20 B0EV:0@4VO, DV1@8;OFVO H;C=>G:V2).

I>:C AC48=: 20A:C;VB.

I>:C @5A?V@0B>@=>W A8AB5<8, 3@C4=>W ;:VB:8 B0 A5@54>ABV==O: :0H5;L, V=D5:FVW

25@E=VE 48E0;L=8E H;OE2V, 70::045=VABL =>A0, A8=CA8B, ?>@CH5==O 7 1>:C ?@840B:>28E ?07CE
=>A0, 2V4GCBBO 48A:>@BC C 3>BFV, D0@8=3VB, ;0@8=3VB, 48A?>=5, 1@>=EVB, =>A>20

:@>2>B5G0, @8=VB, 70ABV9=V O28I0 C 48E0;L=8E H;OE0E V ;535=OE.

I>:C H;C=:>2>:8H:>2>3> B@0:BC: 1V;L C 682>BV, =C4>B0, 4V0@5O, 48A?5?AVO, 70?>@, 7C1=89

1V;L, ACEVABL C @>BV,<5B5>@87<, 30AB@8B, 1;N20==O, A8;L=89 70?>@, ?0=:@50B8B.

I>:C 35?0B>1V;V0@=>W A8AB5<8: ?>@CH5==O DC=:FVW ?5GV=:8.

I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: 28?040=O 2>;>AAO, 45@<0B8B, 5@8B@>45@5@8B5<0,
?>G5@2>=V=O H:V@8, ?V428I5=0 GCB;82VABL 4> A2VB;0, A25@1V=O, 28A8?0=O, :@>?82O=0,
=04
I>:C >?>@=>-@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8: <O7>2V AC4><8, 1V;L C A?8=V, 1V;L C
=>30E, 1V2, 1V;L C :>;V=8E B0 ?;5G>28E AC3;>10E,<O7>2>-A:5;5B=89 1V;L, @83V4=VABL >?>@=>-
@CE>2>3> 0?0@0BC, 0@B@0;3VO, 0@B@8B, 1V;L C :C;LH>28E AC3;>10E, :-:A0;3VO, DV1@>;V7.
I>:C =8@>: B0 A5G>282V4=8E H;OEV2: ?>@CH5=O DC=:FVW =8@>;, =V:BC@VO, =8@>:20
=54>AB0B=VABL, G0AB5 A5G>28?CA:0=O, V=D5:FVWA5G>282V4=8E H;OEV2.
I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: 7=865=O ;V1V4>, 5@5:B8;L=0 48ADC=:FVO
/VB5=FVO.
030;L=V @>7;048 B0 @50:FVW C 0AB5=VO, ?V428I5=0 2B><;N20=VABL, 1V;L C 3@C4OE,
3@8?>?>4V1=V A8<8, =01@O:, =01@O: >1;8GGO, 60@, =574C60=O.
57C;LB0B8 4>A;V465=L: 3V?5@:0;VT3;V:5
>1VG=V @50:FVW, ?>2O70=V 7 3V4@>E;>@>BV0784<
I>:C :@>2V B0 ;VW A8AB5<8: 03@0=C;>F8B>7, 0?;0AB8G=0 0=5?5=VO, ?C@?C@0, B@>
<1>F8B>?5=VO, =59B@>?5=VO.
I>:C VW A8AB5<8: 0=0DV;0:B8G=V @50:FVW, H>:.
I>:C >128= V E0@GC20=O: 0=>@5:AVO, 3V?5@3;V:2>B2>@5=O, 3V?5@C@8:5<03=VT=0B@VT
AC20=V 28A>:8E 4>7 <>6;825 ?V428I5=O @V2=V2 ;V?V4V2 :@>2V.
I>:C ?A8EV:8: 157A>=O.
I>:C =5@2>2>W A8AB5<8: F5D0;3VO (3>;>2=89 1V;L).
I>:C >@30=V2 7>@C: B@0=78B>@=0 =5GVB:VABL 7>@C, :A0=B>?AVO.
I>:C AC48=: =5:@>B8G=89 0=3VWB (20A:C;VB, H:V@=89 20A:C;VB).
I>:C @5A?V@0B>@=>W A8AB5<8, 3@C4=>W ;:VB:8 B0 A5@54>ABV==O: @5A?V@0B>@=89
48AB@5A, C B>
I>:C H;C=:>2>:8H:>2>3> B@0:BC: 70?0;5=O A:8=8E 70;>7, ACEVABL C @>BV, A?0?8, =C4>B0,
1;N20=O, 4V0@5O, 70?>@, ?>4@07=5=O A;87>2>W >1>;>=:8 H;C=:0.
I>:C 35?0B>1V;V0@=>W A8AB5<8: V:B5@CA (2=CB@VH=L>?5GV=:>289 E>;5AB07), E>;5F8AB8B,
?0=:@50B8B, 3V?>E;>@57, I> <>65 V=4C:C20B8 ?5GV=:>2C 5=F5D0;>?0BVN 01> ?5GV=:>2C :>
I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: ?V428I5=0 GCB;82VABL 4> A2VB;0, :@>?82O=:0,
B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, A8=4@< !BV25=A0-6>=A>=0, A8AB5<=89 G5@2>=89 2>2G0:.
I>:C >?>@=>-@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8: <O7>2V A?07<8, AC4>8.
I>:C =8@>: B0 A5G>282V4=8E H;OEV2: 3;N:>7C@VO, V=B5@AB8FV0;L=89 =5D@8B, =8@>:20
48ADC=:FVO, =8@>:20 =54>AB0B=VABL, 7=865=O B>;5@0=B=>ABV 4> 3;N:>78.
I>:C @5?@>4C:B82=>W A8AB5<8: 5@5:B8;L=0 48ADC=:FVO/VB5=FVO.
030;L=V @>7;048 B0 @50:FVW C : ?V428I5=O B5@>G5=O.
5@54>7C20=O.
5<0T 40=8E ?@> A?5F8DVG=5 ;V:C20=O ?5@54>7C20=O ?@5?0@0B>7C20=O B5@0?VN A;V4
?@8?8=8B8, 0 70 ?0FVT=B>< A;V4 2AB0=>28B8 A?>AB5@565=O. /:I> ?@5?0@0B ?@89=OB>
=5I>402=>, ?>B@V1=> 28;;8:0B8 1;N20=O V 268B8 70E>4V2, A?@O<>20=8E =0 CAC=5=O
453V4@0B0FVW, 5;5:B@>;VB=8E ?>@CH5=L, ?5GV=:>2>W :<8 B0 0@B5@V0;L=>W 3V?>B5=7VW.
V:C20=O A8<0B8G=5 V ?V4B@8
>70@B0=
0=V ?@> ?5@54>7C20=O ?@5?0@0BC C ;N459 >1<565=V. 09V<>2V@=VH8<8 ?@>O20<8
?5@54>7C20=O T 0@B5@V0;L=0 3V?>B5=7VO, B0EV:0@4VO; 1@048:0@4VO <>65 1CB8 =0A;V4:<
?0@0A8W (203CA=>W) AB8# 28?04:C A8<0B8G=>W 0@B5@V0;L=>W 3V?>B5=7VW ?>:070=0 ?V4B@8
>70@B0= V 9>3> 0:B82=89 <5B01>;VB =5 2840;ONBLAO H;OE>< 35<>4V0;V7C.
V4@>E;>@>BV0784
09G0ABVHV A8<8 ?5@54>7C20=O T =0A;V4:< 45DVF8BC 5;5:B@>;VBV2 (3V?>:0;VTE;>@5=0B@VT
: =043> A5G>284V;5=O (?>;VC@VO, >;V3C@VO), 01> 0=C@VO, 0;:0;>7, ?V428I5=89 @V25=L 07>BC
A5G>28=8 :@>2V (2 >A=>2=>20 =54>AB0B=VABL). @8 >4=>G0A=>784V2 3V?>:0;VTB5=7VN, H>;,
B0:>6 <>6CBL A?>AB5@V30B8AO A;01:VABL, =C4>B0, 1;N20=O, A?@030, A?;CB0=VABL A2V4>
<>ABV, 70?0<>@>G5=O, A?07<8 <O7V2, ?0@5AB57VO, 28A=065=O, @>7;048 A2V4><>ABV.
V4@>E;>@>BV0784 2840;OTBLAO H;OE>< 35<>4V0;V7C, ?@>B5 ABC?V=L 2840;5=O =5
2AB0=>2;5=89.

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

03VB=VABL

V:0@AL:89 70AV1 ?@>B8?>:070=> 70AB>A>2C20B8 203VB=8< 01> 6V=:0<, O:V ?;0=CNBL
70203VB=VB8. /:I> ?V4 G0A ;V:C20==O F8< 70A>1>< ?V4B25@46CTBLAO 203VB=VABL, 9>3>
70AB>AC20==O =5>1EV4=> =5309=> ?@8?8=8B8 V 70

0:B0FVO

=B03>=VAB8 @5F5?B>@V2 0=3V>B5=78=C II (II)

=D>@<0FVO I>4> 70AB>AC20==O ?@5?0@0BC >70?® ;NA ?V4 G0A 3@C4=>3> 3>4C20==O
2V4ACB=O, B><5=4CTBLAO 70AB>A>2C20B8 >70?® ;NA C F59 ?5@V>4. 060=> ?V4V1@0B8
0;LB5@=0B82=89 ?@5?0@0B 7 1V;LH AB01V;L=8< ?@>DV;5< 157?5:8 4;O 70AB>AC20==O ?V4 G0A
3@C4=>3> 283>4>2C20==O, >A>1;82> =>2>=0@>465=8E B0 =54>=>H5=8E 4VB59.

V4@>E;>@>BV0784

V4@>E;>@>BV0784 5:A:@5BCTBLAO C 3@C4=5 <>;>: ;N48=8 C =525;8:V9 :V;L:>ABV. "V07848 C
28A>:8E 4>70E, 28;;8:0NG8 71V;LH5==O 4VC@57C, <>6CBL ?@83=VGC20B8 A5:@5FVN 3@C4=>3>
<>;>:0. 0AB>AC20==O ?@5?0@0BC >70?® ;NA C ?5@V>4 3@C4=>3> 3>4C20==O =5 @5:>
<5=4CTBLAO. /:I> >70?® ;NA 2A5 6 B0:8 70AB>A>2CTBLAO C ?5@V>4 3>4C20==O 3@C44N, 9>3>
4>70 <0T 1CB8 O:><>30 =86G>N, =0A:V;L:8 F5 <>6;82>.

VB8.

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC 4VBO< =5 2AB0=>2;5=V, B>>70?® ;NA =5 A;V4
70AB>A>2C20B8 4VBO

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

>70@B0=

=3V>=52@>B8G=89 =0I@O:

!B0= ?0FVT=BV2 7 0=3V>=52@>B8G=8< =0I@O:>< 2 0=0<=57V (?@8?CE;VABL >1;8GGO, 3C1, 3;>B:8
B0/01> O78:0) =5>1EV4=> ?>ABV9=> :>=B@>;N20B8 (482. @>74V; <>1VG=V @50:FVW)).

@B5@V0;L=0 3V?>B5=7VO B0 2=CB@VH=L>AC48==0 3V?>2>;5

!8<0B8G=0 0@B5@V0;L=0 3V?>B5=7VO, >A>1;82> ?VA;O ?@89>W 4>78, <>65 28=8:=CB8 C
?0FVT=BV2 7 3V?>2>;5 3V?>=0B@VT® ;NA (482. @>74V;8 «!>AV1 70AB>AC20==O B0 4>78» B0
«@>B8?>:070==O»).

;5:B@>;VB=89 48A10;0=A

;5:B@>;VB=89 48A10;0=A G0AB> A?>AB5@V30TBLAO C ?0FVT=BV2 7 ?>@CH5==O< DC=:FVW
=8@>;, =0 B;V FC:@>2>3> 4V015BC 01> 157 =L>3>. 5>1EV4=> @5B5;L=> :>=B@>;N20B8 ?>:07=8:8
:>=F5=B@0FVW :0;VN C ?;072V, 0 B0:>6 ;V@5=AC :@50B8=V=C, >A>1;82> C ?0FVT=BV2 V7

A5@F52>N =54>AB0B=VABN B0 ;V@5=A< :@50B8=V=C C <560E 30-50 <;E28;8=C. 5 @5:>
<5=4CTBLAO >4=>G0A=5 70AB>AC20==O ;>70@B0=C/3V4@>E;>@>BV0784C 7 :0;V9715@V30NG8<8
4VC@5B8:0<8, E0@G>28<8 4>102:0<8 V7 2< :0;VN, 0 B0:>6 7074V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8
70A>10<8 B0 V=HV 2848 270T<>4V9»).

>@CH5==O DC=:FVW ?5GV=:8

\$0@<0:>:V=5B8G=V 40=V A2V4G0BL ?@> B5, I> C ?0FVT=BV2 7 F8@>7< ?5GV=:8 7=0G=>
?V428ICTBLAO :>=F5=B@0FVO ;>70@B0=C C ?;072V, B>70?® ;NA A;V4 70AB>A>2C20B8 7
>15@56=VABN ?0FVT=B0< 7 ;53:8<8 B0 ?>70?® ;NA ?@>B8?>:070=89 4;O ?0FVT=BV2 7 206:8<8
?>@CH5==O<8 DC=:FVW ?5GV=:8 (482. @>74V;8 «!>AV1 70AB>AC20==O B0 4>78»,
«@>B8?>:070==O» B0 «\$0@<0:>:V=5B8:0»).

>@CH5==O DC=:FVW =8@>:

>2V4><;O;>AO ?@> 28?04:8 ?>3V@H5==O DC=:FVW =8@>;, C B>2C =54>AB0B=VABL, 2=0A;V4>:
V=3V1C20==O @5=V=-0=3V>B5=78=-0;L4>AB5@>=>2>W A8AB5<8 (7>:@5<0 C ?0FVT=BV2 7 BO6:>N
A5@F52>N =54>AB0B=VABN 01> VA=CNG>N =8@>2>N 48ADC=:FVTN). /: V ?@8 28:>@8AB0==V
V=H8E ;V:0@AL:8E 70A>1V2, I> 2?;820NBL =0 @5=V=-0=3V>B5=78=-0;L4>AB5@>=>2C A8AB56
?>2V4><;O;>AO ?@> 71V;LH5==O @V2=V2 A5G>28=8 :@>2V B0 :@50B8=V=C A8@>20B:8 :@>2V C
?0FVT=BV2 7 1V;0B5@0;L=8< AB5=>7< =8@>:28E 0@B5@V9 01> AB5=>7< 0@B5@VW T48=>W
=8@>:8. &V 72>W DC=:FVW <>6CBL 1CB8 72>@>B=8<8 ?VA;O ?@8?8=5==O 70AB>AC20==O
?@5?0@0BC.

>70@B0= A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 1V;0B5@0;L=8< AB5=>7< =8@:>28E
0@B5@V9 01> AB5=>7< 0@B5@VW T48=>W =8@:8.

"@0=A?;0=B0FVO =8@:8

>A2V4 70AB>AC20==O ?@5?0@0BC E2>@8<, I> =5402=> ?5@5=5A;8 B@0=A?;0=B0FVN =8@:8,
2V4ACB=V9.

5@28==89 3V?5@0;L4>AB5@>=V7<

0728G09 C ?0FVT=BV2 7 ?5@28==8< 3V?5@0;L4>AB5@>=V7<< =5 A?>AB5@V30TBLAO 2V4?>2V4V
=0 B5@0?VN 0=B83V?5@B5=782=8<8 ?@5?0@0B0<8, <5E0=V7< 4VW O:8E ?>;O30T 2 V=3V1C20==V
@5=V=-0=3V>B5=78=>2>W A8AB5<8. ">AC20==O ?@5?0@0BC >70?® ;NA W< =5 @5:<5=4>20=5.

H5@>10 A5@FO B0 F5@51@>20A:C;O@=V @>7;048

043> B8A:C C ?0FVT=BV2 7 VH5:0@40 01> V=AC;LBC.

!5@F520 =54>AB0B=VABL

?0FVT=BV2 V7 A5@F52>N =54>AB0B=VABN, I> AC?@>2>46CTBLAO 01> =5 AC?@>2>46CTBLAO
?>@CH5==O< DC=:FVW =8@>:, O: V ?@8 70AB>AC20==V V=H8E ?@5?0@0BV2, I> 2?;820NBL =0
@5=V=-0=3V>B5=78=>2C A8AB5W 0@B5@V0;L=>W 3V?>B5=7VW B0 (G0AB> 3>AB@>W) =8@:>2>W
=54>AB0B=>ABV.

!B5=>7 0>@B8 B0 3> :;0?0=0 A5@FO, >1AB@C:B82=0 3V?5@B@>DVG=0 :0@4V>?0BVO

/: V C 28?04:C 7 V=H8<8 AC48=>@>7H8@N20;L=8<8 70A>10<8, 70AB>A>2C20B8 ?@5?0@0B ?0FVT=B0
<, O:V AB@0640NBL =0 AB5=>7 0>@B8 B03> :;0?0=0 A5@FO 01> >1AB@C:B82=C 3V?5@B@>DVG=C
:0@4V>?0BVN, A;V4 7 >A>1;82>N >15@56=VABN.

?;82 D0:B>@V2 5B=VG=>3> E0@0:B5@C

/: V 2AV V=3V1VB>@8 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC, ;>70@B0= B0 V=HV
0=B03>=VAB8 0=3V>B5=78=C 7=0G=><5=H 5D5:B82=V 4;O 7=865==O 0@B5@V;L=>3> B8A:C C
?@54AB02=8:V2 =53@>W4=>W @0A8, =V6 C ?@54AB02=8:V2 V=H8E @0A. >6;82>, F5 7C<>2;5=> B8<,
I> C ?>?C;OFVW B5<=>H:V@8E ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN ?5@52060T
=87L:>@5=V=>20 D>@<0 0@B5@V0;L=>W 3V?5@B5=7VW.

03VB=VABL

5 A;V4 70AB>A>2C20B8 0=B03>=VAB8 @5F5?B>@V2 0=3V>B5=78=C II (II) O: ?>G0B:>2C B5@0?VN C
?5@V>4 203VB=>ABV. /:I> ?@>4>265==O B5@0?VW ?@5?0@0B0<8 II =5 287=0=> 2:@09 =5>1EV4=8<,
?0FVT=B>;, O:V ?;0=CNBL 70203VB=VB8, A;V4 ?5@525AB8 =0 0;LB5@=0B82=89
0=B83V?5@B5=782=89 ;V:0@AL:89 70AV1 7 ?V4B25@465=8< ?@>DV;5< 157?5:8 4;O 70AB>AC20==O C
?5@V>4 203VB=>ABV.

@07V 4V03=>ABC20==O 203VB=>ABV II A;V4 =5309=> 2V41EV4=>ABV, ?@87=0G8B8
0;LB5@=0B82=C B5@0?VN (482. @>74V;8 «@>B8?>:070==O» B0 «0AB>AC20==O C ?5@V>4
203VB=>ABV 01> 3>4C20==O 3@C44N»).

V4@>E;>@>BV0784

@B5@V0;L=0 3V?>B5=7VO B0 ?>@CH5==O 2>4=>-5;5:B@>;VB=>3> 10;0=AC

/: V ?@8 ?@89>1V2, C 45O:8E ?0FVT=BV2 <>65 A?>AB5@V30B8AO A8<0B8G=0 0@B5@V0;L=0
3V?>B5=7VO. 0FVT=B8 ?>28==V ?5@51C20B8 ?V4 =03;O4< 7 <5B>N A2>TG0A=>3> 28O2;5==O
;;V=VG=8E >7=0: ?>@CH5==O 2>4=>-5;5:B@>;VB=>3> 10;0=AC, =0?@8;;04, 7=52>4=5==O,
3V?>=0B@VTE;>@53> 0;;>7C, 3V?><03=VT 3V?>:0;VT # B0:8E ?0FVT=BV2 =5>1EV4=>

74V9A=N20B8 :>=B@>;L @V2=O 5;5:B@>;V BV2 A8@>20B:8 :@>2V.# ?0FVT=BV2, O:V AB@0640NBL
=0 =01@O:8, C 60@:C ?>3>4C <>65 @>728=CB8AO 3V?>=0B@VT72545==O.

5B0I>;VG=V B0 5=4>:@8==V 5D5:B8

"5@0?VO BV07840<8 <>65 ?>@CHC20B8 B>;5@0=B=VABL 4> 3;N:>78. # 45O:8E 28?04:0E<>65
7=04>18B8AO :>@5:FVO 4>78 3V?>3;V:51V2, C B>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8
B0 V=H8 2848 270T<>4V9»). V4 G0A B5@0?VW BV07840<8 FC:@>289 4V015B <>65 7 ;0B5=B=>W D>@
<8 ?5@59B8 C O2=> 28@065=C.

"V07848 <>6CBL 7<5=HC20B8 282545==O :0;LFVN V7 A5G5N B0 A?@8G8=OB8 5?V7>48G=5 B0
=57=0G=5 ?V428I5==O @V2=O :0;LFVN A8@>20B:8 :@>2V.8@065=0 3V?5@:0;LFVT "@510 ?@8?8=8B8
?@89>< BV0784=>3> 4VC@5B8:0 ?5@54 4>A;V465==O< DC=:FV9 ?0@0I8B>284=8E 70;>7.

V428I5==O @V2=O E>;5AB5@8=C B0 B@83;VF5@84V2 :@>2V B0:>6 <>65 1CB8 ?>2O70=5 7
B5@0?VTN BV0784=8<8 4VC@5B8:0<8.

45O:8E ?0FVT=BV2 B5@0?VO BV07840<8 <>65 ?@8A:>@N20B8 @>728B>: 3V?5@C@8:5 ?>403@8.
A:V;L:8 ;>70@B0= 7=86CT @V25=L A5G>2>W :8A;>B8, ;>70@B0= C :<1V=0FVW 7
3V4@>E;>@>BV0784>< 7<5=HCT ?@>O28 3V?5@C@8:5
>@CH5==O DC=:FVW ?5GV=:8
"V07848 A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 ?>@CH5==O< DC=:FVW ?5GV=:8 01> 7
?@>3@5ACNG8< 70E2>@N20==O< ?5GV=:8, >A:V;L:8 2>=8 <>6CBL 28;:8:0B8 ?>O2C
2=CB@VH=L>?5GV=:>2>3> E>;5AB07C, V =525;8:V 2V4E8;5==O 2V4 =>@<8 7 1>:C @V48==>3> B0
5;5:B@>;VB=>3> 10;0=AC <>6CBL ?@8A:>@N20B8 28=8:=5==O ?5GV=:>2>W :<8.
@5?0@0B >70?® ;NA ?@>B8?>:070=89 ?0FVT=B0< 7 B06:8<8 ?>@CH5==O<8 DC=:FVW ?5GV=:8 (482.
@>74V;8 «@>B8?>:070==O» B0 «\$0@<0>:V=5B8:0»).

01>@0B>@=V 4>A;V465==O
@5?0@0B <>65 7=86C20B8 @V25=L 9>4C C ?;072V. V:C20==O ?@5?0@0B< A;V4 ?@8?8=8B8 ?5@54
?@>2545==O< ;01>@0B>@=>3> >1AB565==O 7 <5B>N >FV=:8 DC=:FVW ?0@0I8B>284=8E 70;>7. &59
;V:0@AL:89 70AV1 740B=89 ?V428IC20B8 :>=F5=B@0FVN 2V;L=>3> 1V;V@C1V=C 2 A8@>20BFV
:@>2V.
=HV 5D5:B8

?0FVT=BV2, O:V 70AB>A>2CNBL BV0784=V 4VC@5B8:8, @50:FVW 3V?5@GCB;82>ABV <>6CBL
A?>AB5@V30B8AO =02VBL C 28?04:C 2V4ACB=>ABV ?@>O2V2 0;5@3VW 01> 1@>=EV0;L=>W 0AB
<8 2 0=0<=57V. ?>2V4><;5==O ?@> @>728B>: 703>AB@5==O 01> ?@>3@5AC20==O A8AB5<=>3>
G5@2>=>3> 2>2G0:C ?@8 70AB>AC20==V BV0784=8E 4VC@5B8:V2.
>?>28=8
&59 ;V:0@AL:89 70AV1=A> 4R, O:89 <>65 28;:8:0B8 0;5@3VG=V @50:FVW.

**40B=VABL 2?;820B8 =0 H284:VABL @50:FV9 ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>1>BV 7
V=H8<8 <5E0=V7<0<8.**

>A;V465=L I>4> 282G5==O 2?;82C =0 740B=VABL :5@C20B8 B@0=A?>@B=8<8 70A>10<8 B0
?@0FN20B8 7 <5E0=V7<0<8 =5 ?@>2>48;>AO. 4=0: ?0FVT=B0<, O:V ?;0=CNBL :5@C20B8
B@0=A?>@B<< 01> ?@0FN20B8 7 <5E0=V7<0<8, A;V4 ?0<OB0B8, I> =0 B;V 0=B83V?5@B5=782=>W
B5@0?VW V=>4V <>6CBL 28=8:0B8 70?0<>@>G5==O 01> A>=:82VABL, 7>:@5<0 =0 ?>G0B:C
;V:C20==O B0 ?@8 71V;LH5==V 4>78.

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

>70@B0=
>2V4><;O;>AO, I> @8D0=07>; 7=86CNBL @V25=L 0:B82=>3><5B01>;VBC. ;V=VG=V =0A;V4:8 F8E
270T<>4V9 =5 282G5=V.
>T4=0==O ;>70@B0=C, O: V V=H8E 70A>1V2, I> 1>;:CNBL 0=3V>B5=78= II 01> 9>3> 5D5:B8, 7
:0;V9715@V30NG8<8 4VC@5B8:0<8 (=0?@8;:04, A?V@>=>;0:B>=, B@V0@84), <>6CBL ?@872>48B8 4>
?V428I5==O @V2=O :0;VN 2 A8@>20BFV :@>2V.!C?CB=T 70AB>AC20==O B0:8E 70A>1V2 =5 @5:>
<5=4>20=5. /: V C 28?04:C 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, O:V ?>3V@HCNBL 282545==O =0B@VN 7
>@30=V7 ?;0=CTBLAO AC?CB=T 22545==O A>;59 ;VBN B0 0=B03>=VABV2 @5F5?B>@V2
0=3V>B5=78=C II, =5>1EV4=> @5B5;L=> :>=B@>;N20B8 A8@>20B:>2V @V2=V ;VBN.
@8 70AB>AC20==V 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C II @07< 7 =5AB5@>W4=8<8
?@>B870?0;L=8<8 ?@5?0@0B0<8 () (=0?@8;:04, A5;5:B82=8<8 V=3V1VB>@0<8 ?A0;VF8;>2>N
:8A;>B>N C ?@>B870?0;L=8E 4>70E) B0 =5A5;5:B82=8<8 <>6;825 ?>A;01;5==O 0=B83V?5@B5=782=>3>
5D5:BC. 4=>G0A=5 70AB>AC20==O 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C II 01>
4VC@5B8:V2 B0 <>65 ?@8725AB8 4> ?V428I5==O @878:C ?>3V@H5==O DC=:FVW =8@>;, C B>
<>6;82>W 3>AB@>W =8@>:2>W =54>AB0B=>ABV, 0 B0:>6 4> ?V428I5==O :>=F5=B@0FVW :0;VN 2
A8@>20BFV :@>2V, >A>1;82> C ?0FVT=BV2 7 VA=CNG>N 7=865=>N DC=:FVTN =8@>: "0:C :>
<1V=0FVN ;V:0@AL:8E 70A>1V2 A;V4 70AB>A>2C20B8 7 >15@56=VABN, >A>1;82> ?0FVT=B0<
;VB=L>3> 2V:C. 0FVT=B ?>28=5= >B@8AB0B=L> @V48=8, B0:>6 A;V4 @>73;O=CB8 <>6;82VABL
:>=B@>;N DC=:FVW =8@>: >4@07C ?VA;O ?>G0B:C >4=>G0A=>3> 70AB>AC20==O F8E ?@5?0@0BV2
B0 ?5@V>48G=> C ?>40;LH>

45O:8E ?0FVT=BV2 7 ?>@CH5=>N DC=:FVTN =8@>;, O:V ;V:C20;8AO (2;:NG0NG8 A5;5:B82=V
V=3V1VB>@8 F8;:>;:A835=078-2), B5@0?VO 0=B03>=VAB0<8 @5F5?B>@V2 0=3V>B5=78=C II <>65
A?@8G8=OB8 ?>40;LH5 ?>3V@H5==O DC=:FVW =8@>: &V 5D5:B8 70728G09 >1>@>B=V.

=HV @5G>28=8, I> 28::8:0NBL 0@B5@V0;L=C 3V?>B5=7VN, B0:V O: B@8F8::VG=V
0=B845?@5A0=B8, 0=B8?A8E>B8:8, 10::>D5=, 0AB8=: ?@8>4=>G0A=>AC20==V 7 F8<8 70A>10<8, O:V
A?@8ONBL 7=865==N 0@B5@V0;L=>3> B8A:C G5@57 B5@0?52B8G=89 5D5:B 01> ?>1VG=V 5D5:B8,
<>65 ?V428IC20B8AO @878: 28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW.
>42V9=0 1;>:040 (=0?@8::04, ?@87=0G5==O V=3V1VB>@0 \$ 7 0=B03>=VAB< @5F5?B>@V2
0=3V>B5=78=C) ?>28==0 >1<56C20B8AO >:@5<> 287=0G5=8<8 28?04:0<8 7 @5B5;L=8< :>=B@>;5<
0@B5@V0;L=>3> B8A:C, DC=:FVW =8@>: B0 @V2=O 5;5:B@>;VBV2. # ?0FVT=BV2 V7
0B5@>A::5@>7<<, A5@F52>N =54>AB0B=VABN 01> FC:@>28< 4V015B< 7 C@065==O< >@30=V2-
42V9=0 1;>:040 @5=V=-0=3V>B5=78=-0;L4>AB5@>=>2>W A8AB5<8 ?>2O7CTBLAO 7 1V;LH 28A>:>N
G0AB>B>N 28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW, =5?@8B<=VABN, 3V?5@:0;VT@CH5==O<
DC=:FVW =8@>: (2::NG0NG8 3>AB@C =8@>:2C =54>AB0B=VABL) ?>@V2=O=> V7 70AB>AC20==O<
>4=>3> 70A>1C.
5 A;V4 70AB>A>2C20B8 0;VA:V@5= >4=>G0A=> 7□>70?® ;NA ?0FVT=B0< 7 FC:@>28< 4V015B>
AC20==O 0;VA:V@5=C @07< 7 ?@5?0@0B< ?0FVT=B0< 7 =8@>:2>N =54>AB0B=VABN (H284:VABL
::C1>G:>2>W DV;LB@0FVW <60 <;E2).
V4@>E;>@>BV0784
@8 ACAC20==V BV0784=8E 4VC@5B8:V2 7:
5B0=>;><, 10@1VBC@0B0<8, =0@:>B8G=8<8 70A>10<8 B0 0=B845?@5A0=B0<8 <>65
?V428IC20B8AO @878: @>728B:C>@B>AB0B8G=>W 0@B5@V0;L=>W 3V?>B5=7VW.
3V?>3;V:5 (?5@>@0;L=8<8 B0 V=AC;V=<<) 70AB>AC20==O BV0784C <>65 2?;820B8 =0
B>;5@0=B=VABL 4> 3;N:>78.>65 7=04>18B8AO :>@5:FVO 4>78 3V?>3;V:51V2. 5BD>@A>2C20B8 7
>15@56=VABN G5@57 @878: 28=8:=5==O ;0:B0B0F84>7C, 28::8:0=>3> DC=:FV>=0;L=>N =8@>:2>N
=54>AB0B=VABN, O:0<>65 28=8:=CB8 ?V4 4VTN 3V4@>E;>@>BV0784C;
V=H8<8 0=B83V?5@B5=782=8<8 70A>10<8 048B82=89 5D5:B;
E>;5AB8@028<8 B0 :>;5AB8?>;>28<8 A<>;0<8 C ?@8ACB=>ABV 0=V>==8E >1
3V4@>E;>@>BV0784C ?>A;01;NTBLAO. 07>2V 4>78 E>;5AB8@028E B0 :>;5AB8?>;>28E A<>;
72O7CNBL 3V4@>E;>@>BV0784 V 7<5=HCNBL 9>3> CA<:BC20==O C H;C=:>2>:8H:>2>B@0:BV =0
85 V 43 % 2V4?>2V4=>;
:>@B8:>AB5@>W40<8, " 28@065=5 7=865==O @V2=O 5;5:B@>;VBV2, 7>:@5<0 3V?>:0;VT
?@5A>@=8<8 0 <>6;825 7=865==O 28@065=>ABV 2V4?>2V4V =0 70AB>AC20==O ?@5A>@=8E 0
AB0B=T 4;O B>3>, I>1 28::NG8B8 WE=T 70AB>AC20==O;
@5;0:A0=B0<8 =545?>;O@87CNG>3> B8?C 4VW (=0?@8::04, BC1>:C@0@8=><) <>6;825 ?>A8;5==O
5D5:BC @5;0:A0=BC;
;VBVT< 4VC@5B8:8 7=86CNBL =8@>:289 ;V@5=A ;VBVN B0 ?V428ICNBL @878:28=8:=5==O
B>:A8G=>W 4VW ;VBVN; WE :<1V=>20=5 70AB>AC20==O =5 @5:><5=4CTBLAO.
V:0@AL:V 70A>18 4;O ;V:C20==O ?>403@8 (?@>15=5F84, AC;LDV=?V@07>= B0 0;>?C@8=>;)
>65 7=04>18B8AO :>@5:FVO 4>78 C@8:>7C@8G=8E ;V:0@AL:8E 70A>1V2 (4;O 282545==O A5G>2>W
:8A;>B8 7>@30=V7A:V;L:8 3V4@>E;>@>BV0784 <>65 28::8:0B8 ?V428I5==O @V2=O A5G>2>W
:8A;>B8 C A8@>20BFV :@>2V. >65 7=04>18B8AO 71V;LH5==O 4>78?@>15=5F84C 01>
AC;LDV=?V@07>=C. 4=>G0A=5 22545==O 7 BV07840<8 <>65 71V;LHC20B8 :V;L:VABL 28?04:V2
28=8:=5==O @50:FV9 3V?5@GCB;82>ABV 4> 0;>?C@8=>;C.
=B8E>;V=5@3VG=V 70A>18 (=0?@8::04, 0B@>?V=, 1V?5@845=)
1V;LH5==O 1V>4>ABC?=>ABV BV0784>28E 4VC@5B8:V2 G5@57 7=865==O <>B>@8:8 H;C=:>2>-
:8H:>2>3> B@0:BC B0 H284:>ABV 28?>@>6=5==O H;C=:0.
&8B>B>:A8G=V 70A>18 (=0?@8::04, F8::>D>AD0
"V07848 <>6CBL 7<5=HC20B8 282545==O F8B>B>:A8G=8E ;V:0@AL:8E 70A>1V2 G5@57 =8@:8 B0
?>B5=7VN20B8 WE=V AC?@5A82=V 5D5:B8.
!0;VF8;0B8
@8 70AB>AC20==V A0;VF8;0BV2 C 28A>:8E 4>70E C ?>T4=0==V 7 3V4@>E;>@>BV0784< <>65
?>A8;N20B8AO B>:A8G=89 2?;82 A0;VF8;0BV2 =0 F5=B@0;L=C =5@2>2C A8AB5
5B8;4>?0
0DV:A>20=V >:@52V4><;5==O ?@> 28?04:8 28=8:=5==O 35<>;VB8G=>W 0=54=>G0A=>3>
70AB>AC20==O 3V4@>E;>@>BV0784C B0 <5B8;4>?8.
?>A?>@8=

4=>G0A=5 70AB>AC20==O 7 F8;:>A?>@8=>< <>65 ?V428IC20B8 @878: 3V?5@C@8:5403@>?>4V1=8E
CA:;04=5=L.
;V:>7848 =0?5@ABO=:8
=4C:>20=0 BV0784>< 3V?>:0;VT 3V?><03=VT
V:0@AL:V 70A>18, =0 O:V 2?;820NBL 7=F5=B@0FVW :0;VN 2 A8@>20BFV :@>2V
5:><5=4CTBLAO ?@>2>48B8 ?5@V>48G=89 :>=B@>;L :>=F5=B@0FVW :0;VN 2 A8@>20BFV :@>2V B0
28:>=0==O , :>8 ;>70@B0=/3V4@>E;>@>BV0784 70AB>A>2CNBLAO >4=>G0A=> 7 ;V:0@AL:8<8
70A>10<8, =0 O:V 2?;820NBL 7=F5=B@0FVW :0;VN 2 A8@>20BFV :@>2V (=0?@8:;04, 3;V:>7848
=0?5@ABO=:8 B0 0=B80@8B18) B0 :>;8 C ?>40;LH>A>2CNBLAO ;V:0@AL:V 70A>18, I> 28:;8:0NBL
?>;V<>@D=C H;C=>G:>2C B0EV:0@4VN (torsades de pointes) (C B>18); 3V?>:0;VT@><, I> A?@8OT
@>728B:C torsades de pointes(?>;V<>@D=>W H;C=>G:>2>W B0EV:0@4VW):
0=B80@8B18 ;0AC Ia (EV=V48=, 3V4@>EV=V48=, 487>?V@0
0=B80@8B18 ;0AC III (040@>=, A>B0;>;, 4>D5B8;V4, V1CB8;V4);
45O:V 0=B8?A8E>B8:8 (=0?@8:;04, BV>@84078=, E;>@?@><078=, ;52><5?@><078=, B@8D;C>?5@078=,
F80<5<078=, AC;L?V@84, AC;LB>?@84, 0
V=HV 70A>18 (=0?@8:;04, 15?@848;, F870?@84, 48D5<0=V;, 5@8B@>25==>3> 22545==O,
30;>D0=B@8=, ;0AB8=, ?5=B025==>3> 22545==O).
!>;V :0;LFFVN
"V0784=V 4VC@5B8:8 <>6CBL ?V428IC20B8 A8@>20B:>2V @V2=V :0;LFFVN G5@57 7=865==O 9>3>
282545==O 7 >@30=V7 70AB>AC20==O ?@5?0@0BV2 :0;LFFVN T =5>1EV4=8<, A;V4 :>=B@>;N20B8
@V25=L :0;LFFVN 2 A8@>20BFV :@>2V, 0 B0:>6 2V4:>@83C20B8 4>7C :0;LFFVN.

?;82 ?@5?0@0BC =0 @57C;LB0B8 ;0I>@0B>@=8E 4>A;V465=L
7207:C V7 2?;82>< BV0784V2 =0 <5B01>;V7< :0;LFFVN WE ?@89>< <>65 7 @57C;LB0B8
4>A;V465==O DC=:FVW ?0@0I8B>284=8E 70;>7 (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).
0@10<075?V=
A=CT @878: 28=8:=5==O A8<0B8G=>W 3V?>=0B@VT1EV4=V ;V=VG=89 B0 1V>;>3VG=89 :>=B@>;L.
>4>2=B@0AB=V 70A>18
@8 =002=>ABV >1C<>2;5=>W 4VC@5B8:0<8 453V4@0B0FVW VA=CT ?V428I5=89 @878: 28=8:=5==O
3>AB@>W =8@:>2>W =54>AB0B=>ABV, >A>1;82> ?@8 70AB>AC20==V ?@>4C:BV2 9>4C C 28A>:8E
4>70E. 5@54 22545==O< ?@5?0@0BC =5>1EV4=> :>4=5==O >@30=V7
B5@8F8= B (4;O ?0@5=B5@0;L=>3> 22545==O), :>@B8:>AB5@>W48, 04@5=>:>@B8:>B@>?=89
3>@<>= ("), AB8=>A=V 70A>18 0I> 3;VF8@878= (:@8FV)
V4@>E;>@>BV0784 <>65 ?>3V@HC20B8 5;5:B@>;VB=89 48A10;0=A, 0 A0<5 ?>3V@HC20B8 AB0=
?@8 3V?>:0;VT=0B@VTE;>@57V, ?V428I5=>BC A5G>28=8 2 :@>2V (2 >A=>2=>2V9 =54>AB0B=>ABV).
5B0-1;>:0B>@8 B0 4V07>:A84
4=>G0A=5 70AB>AC20==O BV0784=8E 4VC@5B8:V2, C B>E;>@>BV0784C, 7 15B0-1;>:0B>@0<8 <>65
?V428IC20B8 @878: 3V?5@3;V:5E;>@>BV0784, <>6CBL ?>A8;N20B8 3V?5@3;V:5:A84C.
<0=B048=
"V07848, C B>E;>@>BV0784, <>6CBL 71V;LHC20B8 @878: ?>1VG=8E 5D5:BV2, A?@8G8=5=8E 0
<0=B048=>

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

5E0=V7< 4VW.

>70?® ;NA F5 :><1V=0FVO ;>70@B0=C V 3V4@>E;>@>BV0784C. # ?0FVT=BV2 7 0@B5@V0;L=>N
3V?5@B5=7VTN B0 3V?5@B@>DVTN ;V2>3> H;C=>G:0 ;>70@B0=, >A>1;82> C :><1V=0FVW 7
3V4@>E;>@>BV0784><, 7<5=HCT @878: @>728B:C A5@F52>-AC48==8E 70E2>@N20=L V
;5B0;L=>ABV, I> 1C;> 4>2545=> 70 4>?>>3>N >FV=:8 :><1V=>20=>W G0AB>B8 @>728B:C A5@F52>-
AC48==8E ?>4V9, V=AC;LBC B0 V=D0@:BC :0@40.
>=5=B8 ?@5?0@0BC ?@>O2;ONBL 048B82=89 0=B83V?5@B5=782=89 5D5:B, 7=86CNG8 @V25=L
0@B5@V0;L=>3> B8A:C 1V;LH>NN, =V6 :>65= 7 :>=5=BV2 >:@5<>. =0A;V4>: 4VC@5B8G=>3>
5D5:BC 3V4@>E;>@>BV0784 ?V428ICT 0:B82=VABL @5=V=C ?;07<8 :@>2V (), AB8AB5@>=C,
?V428ICT @V25=L 0=3V>B5=78=C II V 7=86CT @V25=L :0;VN 2 A8@>20BFV :@>2V.@89><
>70@B0=C 1;>:CT 2AV DV7V>;>3VG=V 5D5:B8 0=3V>B5=78=C II V, 2=0A;V4>: ?@83=VG5==O
5D5:BV2 0;L4>AB5@>=C, <>65 A?@8OB8 7<5=H5==N 2B@0B8 :0;VN, ?>2O70=>W V7 70AB>AC20==O

< 4VC@5B8:0.

>70@B0= G8=8BL ?>7C@8G=C 4VN, I> <8=0T 2 @07V 2V4

V4@>E;>@>BV0784 =57=0G=>N N ?V428ICT @V25=L A5G>2>W :8A;>B8 2 :@>2V; :<1V=0FVO

>70@B0=C B0 3V4@>E;>@>BV0784C ?>A;01;NT 3V?5@C@8:5

\$0@<0:>48=0

>70@B0=

>70@B0= F5 A8=B5B8G=89 0=B03>=VAB @5F5?B>@0 0=3V>B5=78=C II (@5F5?B>@V2 B8?C A_T),
?@87=0G5=89 4;O ?5@>@0;L=>3> 70AB>AC20==O. =3V>B5=78= II ?>BC6=0 AC48=>72C6C20;L=0
@5G>28=0 T >A=>2=8< 0:B82=8< 3>@<=>< @5=V=-0=3V>B5=78=>2>W A8AB5<8 B0 287=0G0;L=8<
D0:B>@< C ?0B>DV7V>;>3VW 0@B5@V0;L=>W 3V?5@B5=7VW. =3V>B5=78= II 7207CTBLAO 7
@5F5?B>@0<8 A_T, O:V E 2840E B:0=8= (=0?@8;;04, C B:0=8=0E 3;045=L:8E <07V2 AC48=,
=04=8@:>28E 70;>7, =8@>: B0 A5@FO), I> ?@872>48BL 4> 28=8:=5==O FV;>3> @O4C 206;828E
1V>;>3VG=8E 5D5:BV2, C B>AB5@>=C. =3V>B5=78= B0:>6 AB8;VD5@0FVN ;VB8= 3;045=L:8E
<07V2. >70@B0= A5;5:B82=> 1;>:CT @5F5?B>@8 "1. >A;V465==O<8 *in vitro* B0 *in vivo* 4>2545=>, I>
>70@B0= B0 9>3> D0@<0:>;>3VG=> 0:B82=89 <5B01>;VB :0@1>=>2>W :8A;>B8 E-3174 1;>:CNBL
CAV DV7V>;>3VG=> 206;82V 5D5:B8 0=3V>B5=78=C , =570;56=> 2V4 9>3> 465@5;0 01> ?>E>465==O.
>70@B0= =5 7207CTBLAO 7 @5F5?B>@0<8 V=H8E 3>@<=>V2 V =5 1;>:CT WE 01> V>==V :0=0;8,
206;82V 4;O A5@F52>-AC48==>W @53C;OFVW. @V< B>3>;>70@B0= =5 V=3V1CT \$ (:V=07C) D5@
<5=B, O:89 @>7;;040T 1@048:V=V=. V4?>2V4=>, =5 2V41C20TBLAO ?>A8;5==O =51060=8E 5D5:BV2,
>?>A5@54:>20=8E 1@048:V=V=>

@8 70AB>AC20==V ;>70@B0=C ?@83=VG5==O =530B82=>3> 72>@>B=>3> 2?;82C 0=3V>B5=78=C =0
A5:@5FVN @5=V=C ?@872>48BL 4> ?V428I5==O 0:B82=>ABV @5=V=C ?;07<8 :@>2V (). V428I5==O
28;;8:0T 71V;LH5==O :>=F5=B@0FVW 0=3V>B5=78=C C ?;072V. 572060NG8 =0 71V;LH5==O
:>=F5=B@0FVW F8E @5G>28=, 0=B83V?5@B5=782=0 0:B82=VABL B0 7<5=H5==O :>=F5=B@0FVW
0;L4>AB5@>=C C ?;072V 715@V30NBLAO, I> A2V4G8BL ?@> 5D5:B82=5 1;>:C20==O @5F5?B>@V2
0=3V>B5=78=C . VA;O ?@8?8=5==O ?@89>70@B0=C 7=0G5==O B0 0=3V>B5=78=C 7=86CNBLAO 4>
>?>G0B:>28E @V2=V2 C B@845==89 ?5@V>4.

/: ;>70@B0=, B0: V 9>3> >A=>2=89 0:B82=89 <5B01>;VB, <0NBL 1V;LHC 0DV==VABL 4> @5F5?B>@V2
"1, =V6 4> @5F5?B>@V2 "2. :B82=89 <5B01>;VB C 10-40 @07V2 0:B82=VH89, =V6 ;>70@B0=, ?@8
?5@5@0EC=:C =0 203C.

0 @57C;LB0B0<8 4>A;V465==O, ?@>2545=>3> A?5FV0;L=> 4;O >FV=:8 G0AB>B8 28=8:=5==O :0H;N C
?0FVT=BV2, O:V ?@89<0;8 ;>70@B0=, ?>@V2=O=> 7 ?0FVT=B0<8, O:V >B@8@8 \$, G0AB>B0
28=8:=5==O :0H;N C ?0FVT=BV2, O:V ?@89<0;8 ;>70@B0= 01> 3V4@>E;>@>BV0784, 1C;0 ?@81;87=>
>4=0:>2>N V 2 B>9 65 G0A AB0B8AB8G=> 7=0GCI> =86G>N, =V6 C ?0FVT=BV2, O:V ?@89<0;8
V=3V1VB>@8 \$. @V< B>3>, 7030;L=89 0=0;V7 16 ?>42V9=8E A;V?8E ;V=VG=8E 4>A;V465=L V7
7030;L=>N CG0ABN 4131 ?0FVT=B0 ?>:0702, I> G0AB>B0 A?>=B0==8E ?>2V4<;5=L ?@> 28?04:8
28=8:=5==O :0H;N C ?0FVT=BV2, O:V ?@89<0;8 ;>70@B0= (3,1 %), 1C;0 ?>4V1=>N 4> G0AB>B B0:8E
?>2V4<;5=L C ?0FVT=BV2, O:V >B@8 (2,6 %) 01> 3V4@>E;>@>BV0784 (4,1 %), B>4V O: G0AB>B0
28=8:=5==O :0H;N C ?0FVT=BV2, O:V ?@89<0;8 V=3V1VB>@8 \$, AB0=>28;0 8,8 %.

0AB>AC20==O ;>70@B0=C :0;VN C ?0FVT=BV2, O:V =5 E2>@VNBL =0 FC:@>289 4V015B B0 O:V
AB@0640NBL =0 0@B5@V0;L=C 3V?5@B5=7VN 7 ?@>B5W=C@VTN, 7=86CT @V25=L
?@>B5W=C@VW, 0 B0:>6 D@0:FV9=C 5:A:@5FVN 0;L1C3;>1C;V=C IgG =0 AB0B8AB8G=> 7=0GCIC
25;8G8=C. >70@B0= ?V4B@8G:>2>W DV;LB@0FVW B0 7<5=HCT DV;LB@0FV9=C D@0:FVN ?;07<8
:@>2V. /: ?@028;>, ;>70@B0= 7=86CT :>=F5=B@0FVN A5G>2>W :8A;>B8 2 A8@>20BFV :@>2V
(70728G09 <0,4 <3/4;), V F59 5D5:B T ABV9:8< ?@8 70AB>AC20==V B@820;>W B5@0?VW.

>70@B0= =5 2?;820T =0 @5D;5:A8 2535B0B82=>W =5@2>2>W A8AB5<8 B0 =5 <0T ?@>;=>3>20=>3>
2?;82C =0 :>=F5=B@0FVN =>@5?V=5D@8=C C ?;072V. # ?0FVT=BV2 7 =54>AB0B=VABN ;V2>3>
H;C=>G:0 70AB>AC20==O ;>70@B0=C C 4>70E 25 <3 B0 50 <3 G8=8BL ?>78B82=89 35<>48=03>@
<=>0;L=89 5D5:B, O:89 E0@0:B5@87CTBLAO ?V428I5==O< V=45:AC >1T<=>W H284:>ABV :@>2>B>:C
A5@FO B0 7=865==O< B8A:C C :V=F528E :0?V;O@0E ;535=V2, 7<5=H5==O< A8AB5<=>3> AC48==>3>
>?>@C, 7=865==O< A5@54=L>3> A8AB5<=>3> 0@B5@V0;L=>3> B8A:C B0 H284:>ABV A5@F528E
A:>@>G5=L, 0 B0:>6 7<5=H5==O< @V2=V2 F8@:C;NNG8E C :@>2V 0;L4>AB5@>=C B0
=>@5?V=5D@8=C 2V4?>2V4=>. # B0:8E ?0FVT=BV2 V7 A5@F52>N =54>AB0B=VABN G0AB>B0
28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW 1C;0 4>70;56=>N.

>A;V465==O C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN

:=B@>;L>20=8E ;;V=VG=8E 28?@>1C20==OE 70AB>AC20==O ;>70@B0=C 1 @07 =0 4>1C C
?0FVT=BV2 7 ;53:>N 01> ?>N ?5@28==>N 0@B5@V0;L=>N 3V?5@B5=7VTN 4>72>;O;> 4>AO3B8
AB0B8AB8G=> 7=0GCI>3> 7=865==O A8AB>;VG=>3> B0 4V0AB>;VG=>3> B8A:C. 83> B8A:C G5@57
24 3>48=8 ?VA;O ?@89>78 ?>@V2=O=> V7 9>3> 28 4>78 ?@>45<=>AB@C20;>; I> 5D5:B 7=865==O
0@B5@V0;L=>3> B8A:C B@820T C?@>4>26
24 3>48=. @8@>4=89 4>1>289 @8B< >@30=V73> B8A:C =0?@8:V=FV V=B5@20;C <0<8 42>E 4>7
AB0=>28BL 70-80 % 5D5:BC, I> A?>AB5@V30TBLAO G5@57 5-6 3>48= ?VA;O ?@89>78.
@8?8=5==O 70AB>AC20==O ;>70@B0=C C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN =5
?@872>48BL 4> @0?B>2>3> ?V428I5==O 0@B5@V0;L=>3> B8A:C (D5=<5= @8:>H5BC). 572060NG8
=0 B5, I> ;>70@B0= 28;;8:0T 28@065=5 7=865==O 0@B5@V0;L=>3> B8A:C, 2V= ACBBT2> =5 2?;820T
=0 G0AB>BC A5@F528E A:>@>G5=L.
>70@B0= >4=0:>2> 5D5:B82=89 C ?0FVT=BV2 G>;>2VG>W B0 6V=>G>W AB0BV, 0 B0:>6 C >AV1
<>;>4>3> (2V:< 4> 65 @>:V2) B0 AB0@H>3> 2V:C, O:V AB@0640NBL =0 0@B5@V0;L=C
3V?5@B5=7VN.

V4@>E;>@>BV0784

V4@>E;>@>BV0784 T BV0784=8< 4VC@5B8:>4=>G0A=5 70AB>AC20==O 0=B03>=VABV2
@5F5?B>@C 0=3V>B5=78=C II <>65 A?@8G8=8B8 72>@>B=>N 2B@0BC :0;VN, ?>2O70=C 7
70AB>AC20==O< BV0784=8E 4VC@5B8:V2.
VA;O ?5@>@0;L=>3> ?@89>7?>G8=0TBLAO C 42>3>48==89 ?5@V>4, 4>AO30T <0:A8 G5@57 4 3>48=8
V B@820T ?@81;87=> 2V4 6 4> 12 3>48=. =B83V?5@B5=782=89 5D5:B 715@V30TBLAO 4> 24 3>48=.
\$0@<0:>:V=5B8:0.

1A>@1FVO

>70@B0=
@8 ?5@>@0;L=>70@B0= 4>1@5 2A<:BCTBLAO B0 ?V440TBLAO <5B01>;V7E>465==V» G5@57
?5GV=:C, 2=0A;V4>: G>3> CB2>@NTBLAO 0:B82=89 :0@1>:A8;L>20=89 <5B01>;VB B0 =50:B82=V
<5B01>;VB8. !8AB5<=0 1V>4>ABC?=VABL ;>70@B0=C C B01;5B>20=V9 D>@28BL ?@81;87=> 33 %.
!5@54=V <0:A8<0;L=V :=F5=B@0FVW ;>70@B0=C V 9>3> 0:B82=>3> <5B01>;VBC 4>AO30NBLAO
G5@57 1 3>48=C V G5@57 3-4 3>48=8 2V4?>2V4=>. @8 70AB>AC20==V ;>70@B0=C ?V4 G0A
728G09=>3> ?@89> 7=0GCI>3> 2?;82C =0 ?@>DV;L :=F5=B@0FVW ;>70@B0=C C ?;072V 28O2;5=> =5
1C>;.

>7?>4V;

>70@B0=
>70@B0= V 9>3> 0:B82=89 <5B01>;VB 72O7CNBLAO 7 1V;;0<8 ?;07<8 :@>2V (2 >A=>2=<) 1V;LH5
=V6 =0 99 %. 1AO3 @>7?>4V;C ;>70@B0=C AB0=>28BL34 ;. >A;V465==O =0 IC@0E ?>:070;8, I>
>70@B0= ?@0:B8G=> =5 ?@>=8:0T :@V7L 35<0B>5=F5D0;VG=89 10@T@.

V4@>E;>@>BV0784

V4@>E;>@>BV0784 ?@>=8:0T :@V7L ?;0F5=B0@=89 (0;5 =5 35<0B>5=F5D0;VG=89) 10@T@ V 2
3@C4=5 <>;>:.

V>B@0=AD>@<0FVO

>70@B0=
@81;87=> 14 % 4>78 ;>70@B0=C ?5@5B2>@NTBLAO =0 9>3> 0:B82=89 <5B01>;VB. VA;O
?5@>@0;L=>3> 22545==O ;>70@B0=C, 3> 14!, @04V>0:B82=VABL F8@:C;NNG>W ?;07<8 =0A0
?>2O70=0 7 =0O2=VABN C =V9 ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC.
@V< 0:B82=>3> <5B01>;VBC, CB2>@NNBLAO 1V>;>3VG=> =50:B82=V, C B>A=>2=8E <5B01>;VB8, I>
CB2>@NNBLAO 2=0A;V4>: 3V4@>:A8;N20==O 1CB8;>2>3> 1VG=>3> ;0=FN30, V >48=
4@C3>@O4=89 N-2-B5B@07>;-3;N:C@>=V4.

82545==O

>70@B0=
;07<>289 ;;V@5=A ;>70@B0=C V 9>3> 0:B82=>3> <5B01>;VBC AB0=>28BL ?@81;87=> 600 <;/E2 V
50 <;/E2 2V4?>2V4=>. 8@:>289 ;;V@5=A ;>70@B0=C V 9>3> 0:B82=>3> <5B01>;VBC AB0=>28BL
?@81;87=> 74 <;/E2 V 26 <;/E2 2V4?>2V4=>. @8 ?5@>@0;L=>70@B0=C <0965
4 % 4>78 282>48BLAO C =57 >70@B0= V 9>3> 0:B82=89 <5B01>;VB <0NBL ;V=V9=C D0@
<0:>:V=5B8:C ?@8 ?5@>@0;L=>70@B0=C C 4>70E 4> 200 <3.

VA;O ?@89>@8 ?@89>2V.
>70@B0= V 9>3> <5B01>;VB8 282>4OBLAO V7 6>2GN B0 A5G5N. VA;O ?5@>@0;L=>3>?@89>
70@B0=C, 3> 14!, ?@81;87=> 35 % @04V>0:B82=>ABV 28O2;OTBLAO C A5GV B0 58 % C :0;V.
V4@>E;>@>BV0784
V4@>E;>@>BV0784 =5 ?V440TBLAO <5B01>;V7 282>48BLAO =8@:0<8. @8 :>=B@>;V @V2=O
?@5?0@0BC C ?;07 :@>2V ?@>BO3>< O: 24 3>48=8 ?5@V>4 =0?V2282545==O 20@VN202 2V4
5,6 4> 14,8 3>48=8. 5 <5=H5 61 % ?@89=OB>W 4>78 282>48;>AO C =57BO3>< 24 3>48=.

%0@0:B5@8AB8:8 C ?0FVT=BV2
>70@B0=-□ V4@>E;>@>BV0784
>=F5=B@0FVW ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VB0 C ?;072V, 0 B0:>6 @V25=L 2A
<>:BC20==O 3V4@>E;>@>BV0784C C ?0FVT=BV2 ;VB=L>3> 2V:C 7 0@B5@V0;L=>N 3V?5@B5=7VN
AB0B8AB8G=> 7=0GCI> =5 2V4@V7=ONBLAO 2V4 F8E ?>:07=8:V2 C <>;>48E ?0FVT=BV2 7
0@B5@V0;L=>N 3V?5@B5=7VTN.
>70@B0=
?0FVT=BV2 7 ;53:8< 01> ?>2V ?VA;O ?5@>@0;L=>3> 70AB>AC20==O 1C;8 2V4?>2V4=> C
5 B0 1,7 @07C 28I8<8, =V6 C <>;>48E 74>@>28E 4>1@>2>;LFV2 G>;>2VG>W AB0BV. =V ;>70@B0=,
0=V 9>3> 0:B82=89 <5B01>;VB =5 282>4OBLAO ?@8 35<>4V0;V7V.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.
A=>2=V DV78:>-EVABV: 6>2BV >20;L=V B01;5B:8, 2:@8BV >1>;>=:>N, 7 @8A:>N 7 >1>E 1>:V2.

5AC 52V4><0.

"5@ABV. 2 @>:8.

#<>28 715@V30==O. 15@V30B8 2 >@83V=0;L=V9 C?0:>2FV, 2 =54>ABC?=>?@8 B5=5 28I5 30 °!.

#?0:>2:0. 10, 30 (10E3), 30 (15E2), 90 (10E9), 90 (15E6):
?> 10 B01;5B>: C 1;VAB5@V; ?> 1, 3 01> 9 1;VAB5@V2 C :0@B>==V9 :>@>1FV
?> 15 B01;5B>: C 1;VAB5@V; ?> 2 01> 6 1;VAB5@V2 C :0@B>==V9 :>@>1FV.

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

8@>1=8:.
"«5=BV20» /
Zentiva k.s.

VAF57=0E>465==O.
:015;>2=8 130, 102 37 @030 10, >;=V TE>;C?8, '5AL:0 5A?C1;V:0 /
U kabelovny 130, 102 37 Praha 10, Dolni Mecholupi, Czech Republic.