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

®
(PROPANORM®)

!:;04:

4VNG0 @5G>28=0: ?@>?0D5=>=C 3V4@>E;>@@@84;

1 B01;5B:0 ?0D5=>=C 3V4@>E;>@@@84C 150 <3 01> 300 <3;

4>?>28=8: F5;N;>70 :@8AB0;;VG=0, =0B@VN :@>A:0@<5;>70, =0B@VN ;0C@8;AC;L4D0B, :@@>E<0;L :C:C@C47O=89, :>?>?2V4>=, <03=VN AB50@0B, opadry white 02F 28310 (3V?@>?><5;>70, B8B0=C 4V>:A84 (171), ?@>;V5B8;5=3;V:>;;),5

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

A=>2=2=V DV78:>-EVABV: <0965 1V;V B01;5B:8, 2:@8BV >1>;>=:>N, 42>>?C:;V, 4V0<5B@@>< 1;87L;> 8 << (B01;5B:8 ?> 150 <3) B0 1;87L;> 11 << (B01;5B:8 ?> 300 <3).

$0@<0:>B5@0?52B8G=0 3@C?0. @5?0@0B8 4;O ;V:C20==O 70E2@>@N20=L A5@FO. =B80@8B<   !. >4 " % !01!03.

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

$0@<0:>:;>48=0<8:0

@>?0D5=>= T 0=B80@8B<

V= G8=8BL AB01V;V;V7CNGC 4VN =0:0@4V0;L=C <5<1@0=0=8, 7<5=HCT H284:89 2EV4=89 AB@@C<C, I> ?@@>2>48BLAO V>=0<8 =0B@VN, 7V 7<5=H5==O< H284:>ABV 45?>;O@870FVW B0 ?>4>26CT G0A ?@>2545==O V ?5@54A4A@4N, AV-2C7;C B0 3>;>2==O< G8=>< ?> ?@>2V4=V9 A8AB5 @>2545==O V 4>40B:>28E H;OE0E, O: ?@8 A8=C=>< >:LD0-0@:V==>-#09B0), ?@@83=>=GCTBL AO 7024O:8 ?@>;>>=30FVW @5D@0:B5@=>3> ?5@V>4C 01> 1;>:04V ?@>2V4=>>3> H;OEC O: 2 0=B53@04=>< => C @5B@>3@04=> C @5B@>3@04=>

07>< 7 B8< A?@>=>==0 71C46C20==VABL 7=8=86CTBLAO 7024O:8 ?V428I5==N ?@>30:0@4V0;L=>W GCB;82>ABV, B>4V O: 5;5:B@8G=0 71C46C20==VABL:0@4V0 7=8=86CTBLAO 7024O:8 ?V428I5==N ?@>30 25=B@8:C;C;O@=>W DV1@8;OFVW.

@>B80@8B<V2;=5==O H284:>ABV 7@@>AB0==O ?>B5=FV0;C 4VW, 7=865==O 71C46C20==O, 3> <>35=V70FVW :>5DVFVT=0B ?@>2V4=>ABV, ?@83=VG>=3> 5:B>?V>G=>3> 02B><0B87<C :0@40 4> DV1@8;OFVW.

@>?0D5=>= <0T ?>3 7=0G5==O. @@>B5 VA=CT <;565=>, 82VABL, I> 28A>:V 4>1>2V 4>78 (900-1200<3) <>6CBL A?@8G8=8B8 A;VVB;82V=89 (0=B804@5=53VG=89) 5D5:B.

0 ?@>?0D5=>= 28;82;8>B =5?5;5 ?>4265==O V=B5@20;V2, PR B0 QRS, B>4V O: V=B5@20;; Q"A, O: ?@028;>, 70;8H0TBLAO =5757

483VB0;V7>20=8E ?0FVT=B2 7 D@@>:VN 28=84C 35-50 % A:>@>B8=VABL ;V2>3> H;C=>G:0 45I> 7=865=0. # ?0FVT=B2 V7 A3C@B@8T< B01;4> B>5=5==O< H?04C 28A84C ;V2>3> H;C=>G:0, 05 7=0G=0 <5=H0 N 5 2V41<V=C20==O B01;4> C ?0FVT=B2 15 H;C=>G:0 V7 701;>20==O< A5@F52>N =54>AB0BN>==O. >1=5 28?;82V1@8;OF0G V =535=528E B0: C >54=5 50B5 0@B5@V;L=>3> B8ACV:C ?V428I5=0 ?V428I5==O

">A3=0B:>20==O, O:C =5 ;V:C20=8,<>65 =040;V ?@>A8N20B8AO 7 >;O:89=@5:>4>

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

@>?0D5=>= O2;OT A>1>N @0F5<0D5=>=C.

<u>1A>@@1FVO</u>

0:A8<0;L=0 :>=F5=B@0FVO C ?;0A<V 4>A>30TBLAO G5@57 23 3>48=8 ?VA;O ?@>?0D5=>=C 3V4@>E;>@@@84C. B0>>=2;5=>, I> ?@>?0D5=>= 707=0T V=B5=A82=>3> <5B01>;V7<C 70 @0E0E @>E0 ?@8 ?5@H>><C ?@>E>465==V G5@57 ?5G28=:C (CYP2D6-70;56=89 5D5:B ?5@H>3> ?@@>E>465==O G5@57 ?5GV=:C), I> ?@>O2;OTBLAO 70;56=VABN 2V4 4>78 B0 ;V:0@AL:>W D>@<8 ?@5?0@0B0. %>G0 C 4>A;V465==O 70E20@N20=L A5@FO< @07>2>N 4>7>N ?@5?0@0B 2 4V0?07>=V W6V 71V;LHC=202 <>3V 71V;LHC=02 B0: =6V =5 ?@>?>@FV9=> 28=84C 1@>;<C =8 H8@ 3>48=8 3V4@>;>7C 4> DVATBLAO.

>7?>4V;
@>?0D5=>= H284:> @>7?>4V;OTBLAO. 1'T< @>7?>4V;C C @V2=>206=>28BL 2V4 1,9 4> 3,0 ;/:3.
!BC?V=L 72'O7C20==O ?@>?0D5=>=C 7 1V;:0<8 ?;07<8 :@>2V 70;568BL 2V4 9>3> :>=F5=B@0FVW B0 7=86CTBLAO 7 97,3 % ?@8 :>=F5=B@0FVW 0,25 =3/<; 4> 91,3 % ?@8 100 =3/<;.
V>B@0=0=AD>@<0FVO B0 282545==O
A=CT 420 35=5B8G=> >1C<>2;5=8E H;OE8 <5B01>;V7?0D5=>=C. # 1V;LH =V6 90 % ?0FVT=BV2 ?@5?0@0B 707=0T H284:>3> B0 V=B5=A82=>3> <5B01>;V7<C =0?V2V2282545==O 2V4 2 4> 10 3>48= (H284:V <5B01>;V70B>@8). # B0:8E ?0FVT=BV2 <5B01>;V7< >B@8<CT 5 ?5@5B2>@5==O ?@>?0D5=>=C ?@872>48BL 4> CB2>@5==O 42>E 0:B82=8E <5B01>;VB V2: 5-3V4@>:A8?@>?0D5=>=C, I> CB2>@NTBLAO ?V4 4VTN CYP2D6, B0 N-45?@>?V;?@>?0D5=>=C (=>@@?@>?0D5=>=C), I> CB2>@NTBLAO ?V4 4VTN CYP3A4 B0 CYP1A2. # <5=H =V6 10 % ?0FVT=BV2 (?>2V;L=V <5B01>;V70B>@8) <5B01>;V7< ?@>?0D5=>=C 2V41C20TBLAO ?>2V;L=VH5, >A:V;L:8 5-3V4@>:A8?@>?0D5=>=C V ;89 <5B01>;VB5 CB2>@NTBLAO 01> CB2>@NTBLAO C :V;L:>ABOE.
>7?0EC=:>289 ?5@V>4 =0?V2282545==O ?@>?0D5=>=C AB0=>=>28BL
210 3>48= C H284:8E <5B01>;V70B>@V2 B0 1032 3>48=8 C ?>2V;L=8E <5B01>;V70B>@V2. ;V@5=A?@>?0D5=>=C AB0=>=>28BL 2V4 0,67 4> 0,81 ;/3>4/:3.
A:V;L:8 @V2=>=>206=0 :>=F5=B@0FVO ?@>?0D5=>=C 3V4@>E;>@84C 4>AO30TBLAO G5@57 34 4=V ?@89><5=4>20=89 @568<C 4>7C20==O ?@>?0D5=>=C T >4=0:>;>28< 4;O CAVE ?0FVT=BV2 =570;56=> 2V4 B8?C <5B01>;V71B> O: 4;O ?>2V;L=8E, B0: V 4;O H284:8E <5B01>;V70B>@V2).
V=V9=VABL/=5;V=V9=VABL
0A8GC20=89 <5B01>;V7< H;OE 3V4@>:A8;N20==O (70;56=89 2V4 CYP2D6) C H284:8E <5B01>;V70B>@V2 ?@872>48BL 4> =5;V=V9=>ABV D0@<0:>:V=5B8:8 ?@5?0@0BC. # ?>2V;L=8E <5B01>;V70B>@V2 D0@<0:>:V=5B8:0 ?@>?0D5=>=C T ;V=V9=>N.
V6- B0 V=B@0V=482V4C0;L=0 20@V015;L=VABL
;O D0@<0:>:V=5B8:8 ?@>?0D5=>=C 3V4@>E;>@84C E0@0:B5@=0 89 7=0G=0 89 ABC?V=L V=B5@V=482V4C0;L=>W 20@V015;L=>ABV, >:89 7=0G=>NN >1C<>2;5=89 5D5:B>< ?5@H>3> ?@>E>465==O G5@57 ?5GV=:C B0 =5;V=V9=>N D0@<0:>:V=5B8:>N C H284:8E <5B01>;V70B>@V2. '5GV=:>28 7=0G=0 20@V015;L=VABL :>=F5=B@0FVW ?@5?0@0BC C :@>2V ?0FVT=BV2 ?>B@51CT >15@56=>ABV ?@8 ?V418@0==V 4>78, C206=> :>=B@>;N20B8 ::;V=V9=V B0 5;5:B@>:0@4V>3@0DVG=V ?>:07=8:8 B?>:07=8:8 B>:7V:07=8=8B8 B>A8G=>NABV.
0FVT=B8 ;V=;N>3> 2V:C
V2=V 5:A?>78FVW ?@>?0D5=>=C C ?0FVT=BV2 ;V=;N>3> 2V:C 7 =>@<0;L=>N DC=:FVT N DC=:FVT N D=FVT V=FVT V=4@5=>>3> 20@V015=>N<5B01>;V7<C, 70@@>5TAB@>>20=8E C 74>@>28E 4>1@>2>;LFV2. :A?>78FVO 5-3V4@>:A8?@>?0D5=>=C C ;V=;N><C 2VFV 1C;0 AE>6>N, 0;5 @V2=V 5:A?>78FVW 3;N:C@>=V4V2 ?@>?0D5=>=C 7@>AB0;8 242VGV.

>@CH5==O DC=:FVW =8@>:
?0FVT=BV2 7 ?>@CH5==O< DC=:FVW =8@>:: @V2=V 5:A?>78FVW ?@>?0D5=>=C B0 5-3V4@>:A8?@>?0D5=>=C =5 2V4@V7=O;8AO 2V4 @V2=V2, 70@@5TAB@>20=8E C 74>@>28E 4>1@>2>;LFV2 7 =>@<0;L=>N DC=:FVTN =8@>:. :A?>78FVO =>@?@>?0D5=>=C 70;56=>ABV 2V4 =>@?>@CH5==O DC=:FVW =8@>:. 0FVT=B0< V7 =8@:>2>N =54>AB0B=VABN ?@5?0@0B A;V4 ?@870G0B8 V7 >AB>@>6=VABN B0 ?V4 @5B5;L=8< :>=B@>;5<.
>@CH5==O DC=:FVW ?5GV=:8
?0FVT=BV2 7 ?>@CH5==O< DC=:FVW ?5GV=:8 7@>AB0T 1V>4>ABC?=VABL ?@>?0D5=>=C ?@8 ?5@>@0;L=><C ?@89><V B0 ?>4>26CTBLAO ?5@V>4 =0?V2282545==O ?@5?0@0BC. ">@=>28>3> ?5GV=:8 ?>B@51CT@51CT >AB>>:5:FVW 4>78 ?@5?0@0BC.

;V=VG=V E0@0:B5@8AB8:8.
>:070==O.
@>DV;0:B8:0 B0 ;V:C20==O:
· 25=B@8:C;O@=8E 0@8B<V9
· ?0@>:A87<0;L=8E AC?@025=B@8:C;O@=8E B0EV:0@4V9 B0 ?0@>:A87<0;L=8E D>@< D>@C20==O ?5@5408A5@4L B0 ?0@>:A87=0;L=8E =>;V=V :C2 :@>028 >3 B8?C 70;56=>3> 2V4 C>=@>;C20==O< AV-2C7;0 01> 4>40B:>2>3> ?@>2V4=8E H;OE2, ?@8 =55D5:B82=>ABV V=H8E ;V:0@AL:8E 70A>1V2 01> ?@8 =5<>6;8=>ABV WE =8:>@8AB0==O.

@>B8?>:070==O.

- V?5@GCB;82VABL 4> ?@>?0D5=>=C 01> 4> 1C4L-O:>3> V=H>3> :>=5=B0 ?@5?0@0BC.
- 8O2;5=89 A8=4@@>< @C3040 (482. «A>1;82>ABV 70AB>AC20==O»).
- 8?04>: V=D0@:BC :0@40 70 >AB0==V 3
- =0G=5 >@30=VG=5 70E2>@N20==O A5@FO, B0:5 O:::
    =5:>=B@@@>;L>20=0 E@@=VG=0 A5@F520 =54>AB0B=VABL (D@0:FVO 28:84C ;V2>3> H;C=>G:0 <35 %);
    :0@4V>35==89 H>: (O:I> 2V= =5 A?@8G8=5=89 0@8B
- "O6:0 A8<0B8G=0 1@048:0@4VO.
- 5:>=B@@@;L>20=V 5;5:B@@@;VB=V ?>@CH5==O (=0?@8:;04 ?>@CH5==O <5B01>;V7>;C7
- "O6:V >1AB@C:B82=V 70E2>@N20==O ;535=V2.
- "O6:0 0@B5@V0;L=0 3V?>B5=7VO.
- 8ADC=:FVO A8=CA@2>3> 2C7;0, ?>@CH5==O ?5@54A5@4=>=>W ?@>2V4=>ABV, AV-1;>:040 ABC?5=O 01> 28I5, 1;>:040 ?CG:0 VA0 01> 48AB0;L=0 1;>:040 ?@8 2V4ACB=>ABV HBCG=>3> 2>4VO @8B
- 4=>G0A=5 70AB>AC20==O 7 @8B>=02V@>
- V0AB5=VO 3@02VA.
- "O6:0 ?5GV=:>=>20 =54>AB0B=VABL.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.
>1VG=V 5D5:B8 ?@>?>D5=>=C 3V4@0>E;>@84C <>6CBL ?>B5=FVN20B8A0 ?@8 9>3> 70AB>AC20==V C :><1V=0FVW 7 V=H8<8 70A>10<8, I>
?@83=VGCNBL G0AB>BC A5@F528E A:>@>G5=L B0/01> A:>@@>GC20;L=C 740B=VABL:0@40 (=0?@8:;04 15B0-1;>:0B@8, B@8F8:;VG=V 0=B845?@5A0=B8).
4>A;V465==V 7 CG0ABN 8 74>@>28E 4>1@>2>;LFV2, O:V >B@8<?0D5=>= B0 20@D0@8=
>4=>G0A=>, A5@4=V @V2=V @>206=V ?;07<V >A=>=>2V :>=F5=B@0FVW 20@D0@8=C 71V;LHC20;8AO =0 39 %
7 2V4?>2V4=8< 71V;LH5==O< ?@>B@><1V=>2>3> G0AC =0 25 %. @8 >4>G0A=>AC20==V
?@>?>D5=>=C B0 ?5@>@0;L=8E 0=B8:>03C;O=BV2 (=0?@8:;04 D5?@0::C<0@, 20@D0@8=C, 0F5=>:C<0@>;C) =5>1EV4=> @5B5;L=> >B@8<C20B8 73@>B0==O :>2>2V, >A:V;L:8 ?@>?>D5=>==>65
?V428IC20B8 5D5:B82=VABL F8E ;V:0@AL:8E 70A>1V2, 71V;LHCNG8 ?@>B@><1V289 G0A.
5>1EV4=> 2V4?>2V4=> 7<5=H8B8 4>7C 0=B8:>03C;O=BV2, O:I> A@>AB5@3V0NBLAO >7:0:8
?5@>@0;L=7C20==O.
4=>G0A=5 70AB>AC20==O ?@>?>D5=>=C 3V4@0>E;>@84C 7 ;V:0@AL:8<8 70A>10<8, I>
<5B01>;V7CNBLAO 70 4>?><>3>N CYP2D6 (B0:8E O: 25=;0D0:A8=), >65 A?@8G8=8B8 ?V428IC==O
:>=F5=B@0FVW F8E ;V:0@AL:8E 70A>1V2. >2V4><;5=> ?@> ?V428IC==O :>=F5=B@0FVW
?@>?@0=>;>;C, <5B@>?@>;>;C, 4578?@0<V=C, B5>DV;V=C (7 @>728B:>< B5>DV;V=>2>W
B>:A8G=>ABV) B0 483>:A8=C C ?0FV=B 01> C :>2V ?@8 8E >4=>G0A=>AB>AC20==V 7 ?@>?>D5=>==>C
3V4@0>E;>@84C C :><1V=0FVW 7 =878<8 4>78 F8E ;V:0@AL:8E 70A>1V2, O:I> 70 =5>1EV4=>ABV
A?@8G8=8B8 @>728B>: 483>:A8=>2>W B>:A8G=>ABV, O:I> 2V4<V=8B8 B5@0?VN.
V0A:0@4VO 70A>18, I> ?@83=VGCNBL CYP2D6, CYP1A2 B0 CYP3A4, =0?@8:;04 :5B>=>70>;, F8
<5B01>;VCNBL, 5;5V20N=>=, 5@VB@><VF8= ?@8872548B8 4> ?V428IC==O @V2=N 2V@>?>D5=>=C
3V4@0>E;>@84C C :>2V. @8 70AB>AC20==V ?@>?>D5=>=C 3V4@0>E;>@84C 7 V3V1VB>@><8 F8E
D5@<5=BV2 A;V4 @5B5;L=> AB568B8 70 AB0=>< ?0FV=B0 B0 2V4?>2V4=> :>@83C20B8 4>7C.
><1V=>20=0 B5@0?VO 040@>=>< C ?@>?>D5=>==>< <65 ?@87748B8 4> @>728B:C B0:V 5D5:B8
@5A?V@0B>@=>W B0 A5@F5=>W 2848 B5@0?VW, O:I> <05 V3V1VB>@=5 70AB>AC20==O ?@>?>D5=>==>C
3V4@0>E;>@84C B0 ;V4:>=2V@A >1878: >>728B:B >1VG=V 5D5:B8 1V2 20@D0@8=C.
$5=>10@1VB0; T 2V4><8< V=4C:B>@>< CYP3A4. V4 G0A B@82020;>3> :><1V=>20==>3> 70AB>AC20==O
D5=>10@1VB0;C A;V4 AB568B8 70 ;;V=V=>VGN 2V4?>2V44N =0 B5@0?VN ?@>?>D5=>==>
<>728B>=20=5 70AB>AC20==O ?@>?>D5=>==>C 3V4@0>E;>@84C B0 @8D0>4C5 ?>32@@@0??>>B8 ?@>B8=0=8B8
?@>4C@0==O G5@57 7>865==O 9>3> >728F5==0?@>0FVW C ?;07<V (@8878: @>0?B>>728B>: 0=8B
V428I5=V @V2=V ?@>?>D5=>==>C C ;V4:>=2V@A A?@8G8=8=B>1>0=8B ?@>?>D5=>==>C 4=>G0A=>

AC20==V V7 A5;5:B82=8<8 V=3V1VB>@0<8 72>@>B=>3> 70E>?;5==O A5@>B<B>=V=C, B0:8<8 O: D;C>:A5B8= B0 ?0@>:A5B8=. 4=>G0A=5 70AB>AC20==O ?@>?0D5=>C 3V4@@E;>@84C B0 D;C>:A5B8=C C C ?0FVT=BV2 7 5:AB5=A82=8< <5B01>;;;V7>< ?V428IC20;;> C_{max} (<0:A8<0;;;;L=0 :>=F5=B@0FVO C ?;072V) B0 AUC (?;>I0 ?V4 D0@@<@<V=B0@=5B8V=O :@82>B0> N :@82>B>N) S ?@>?0D5=>C =0 39 % B0 50 % 2V4?>2V4=>, 0 C_{max} B0 AUC R ?@>?0D5=>C =0 71 % B0 50 %. ;O 4>AO3=5==O 1060=>3> B5@@0?52B8G=>3> 5D5:BC <>65 1CB8 4>AB0B=L> 70AB>AC20==O <5=H8E 4>7 ?@>?0D5=>C. >15@@56=VABN A;V4 70AB>A>A>2C20B8 ?@>?0D5=>= 7 @>A;8===8 ?@>5?0@0B0<8-<>4C;O@@>@<@0<8 F8B>E@><>

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

!5@F52>>-AC48==0 A8AB5<0@<5<0. 06;82>>, I>1 :>65= ?0FVT=B ?@>E>482 5;5:B@@>:0@@0V>3@>0DVG=5 B0 ::V=VG=5 >1AB565==O ?5@@54 ?>G0B0:>>< B0 ?@@>B>3>B>< B5@@5@@0?VW ® 4;O 287=0G5==O ::V=VG5=>W 5D5:B82=>ABV ;V:@0@>B@0==O B0 =5@>1V1V9>3> ?@>4>265==O.

!;01:89 =530B82=89 V=>B0?;89 5D5:B #® <>65 <01>8 7=0G5==O C ?0FVT=BV2 V7 @878:>< @>728B>B>A A5@F52>@W =54>AB0B=>ABV.

0AB>AC20==O ?@>?0D5=>C <>65 45<>=A:0@0B8 A8=4@@>< @C3040 01> A?@83@8=8B8 2V4?>2V4=8 7 AV1 V7 157A8<>5<8 ?@>@O20<8 FL>3> A8=4@@>@>:C B5@@0?VW ?@>?0D5=>=>< =5>1E2V4>=>> ?@>@>25AB8 B8:>45A?:;NG5==O 7 2>07CNBL =0 A8=4@@>< @C3040.

@>?0D5=>C 3V4@@E;>@84 <>65 7@V3 71C465==O B0 GCB;;82>=>B>ABV HBCG==5 2>4>W2 @8B<V 5D@5:B82=>ABV ?5@F52>@@@B8 V ?@@8 =5@>1V1V9>=>B5< ?@@8 =54>AB0B=>ABV

>B5=FV9=> <>6;82>=8 ?@>@?V28289 ?@@>?0D5=>B?=>?>>A87<>0L=5=> D>B@@@?VW 2V7@@1V?0 5?0B0;5@@4L C B@@>V?>B>B>==O 2:1 01> ?@>@>2V4=>2A5=BN 1:1 (482. «>1VG=V @@50:FVV»).

0FVT=B8 7V 7=0G=8< >@@30=>=>B>0V><> =5@@@0DO @@50:FV9 =0 4@@30B@@> >@@30@<>B @@50V<B ?@@8 =54>AB0B=>ABV 3V4@>E;>@84C ?@>?0D5=>B?>:070=89 B0:< ?@>@?VFV>B<T (482. «@>1V?>B<0@<@<0<>V»).

@>?0D5=> C?>2V;N<T A5@@F52@C ?0FVT<V2V4=2VABL, I<>65 28:;8:0B8 4@7@>;;56=5 ?>4@>265==O V=B52@20;C PR, :>728B>: 0B@V>2=25=@80B@V9=>>W 1;>@:04 ?5@@2>3> 01> 28I>3> ABC?5=O, 1;>:04C =V68:8 ?C:;<V 0B@V9B@V9=>@0>B@< 70B@@@8< B@V68:8 ?C:;<V >@3@0>B4 ?@>@?VFV>T= (482. @>74V; «>1VG=V @@50:FVV»). "0:8< G8=>2< ?@@8 ?@2>2V8 V=B@@@0?VW ?@>@?VFV>B<>< <>65 1CB8 C?>2V;N<2=> ?@>@>265==O ?@V4 G0A A8AB@>;V:C>=>> ?@>0V>B<>B T =5>1V1V9>=>B< ® =5>1V1V9>B< 7<5=H8B8 4>7C 01> 2V4

!8AB5<0=> :@>2>0=>>2V. 5G0AB> ?@@>@@BO <54 ?5@@F5@>B@V9=>@>=>B>, ?@8 ?5@@F5@B@V9=>B8 @C3040 B0 ?@8 =54>@@B>B>=>ABV.

?@@> @>@?V28289 03@>2V=>@?V8 :7C@@>B@@>C, >:89 ?@@>@2;O>?>2A5?< B0:< A8<2B>B>==, O: 30@>B@:C@0, A;01:VABL, =574@4>C60==>, >7@>:89 2>4>W=C. # @>07V< 7=8865==O< :V;L:>ABV B@>>@>@1V7>:C @@0A=4<5@@>@< ?@8?@@@>2>8 701>0=>V 20 0B@@>@>8 ?@@>2;O>>A0 A8<2?B>B>< 7=V6:8:C =54>AB0B=>@ABV 2>4>W. B0 >@?>:89 :7C@@>B@@>C :2V;L:>ABV V> ?@@8 30@>B<B@:C@0 >0< 2V@?5<= @07; N=5 2A5@>@<>:=>> 70@@0<A87>07C@@5 :@0B@V9=?@>B>B 453@9 :@0B@V9=?@>0:CNBL ®.

V40=>=>T @0:2V1:C, :@0V>B>2V 7@>V3 71C765=== HBCG=<=5 >0A@0V8 @8B<V 42>@>@>B<>@>@@>@>B8 T @@5@30@>?=>T ?@>@>0>B>O :@0:2V4=>0A :@@0 7@>V3 71C765==O 70AB>AC20==O ?@>@>AV1C.

5@@B>B>1>1V>>V28T;V0@@< 0 A8AB5<0<V. @@>@?V28289 03@>@2V=>@?V8 :7C@@>B@@>C, A;V4 70AB>A>C2CN2C20B8 ?@>@?V28289 <5=H5 ?@@@>>@7C.

0AB>AC20==O C ?5@@V>@>4 203VB=>AB>B8 01> 3@>4C20==O 3@>C44NN.

>A;V4@65==O =0 B20@8=0E 8 E;5 28>@0828;; B0@>@>8 B<>@V4>B0? 4VW. 45:2>0B=> 45:2>2@5V==8 B>@>@<>>>@>B>T 40>@4>V@>?>2A5=>> 70AB>AC20==O FL>3> ;V:@0@>B@0>@>B<=0 20B=V1B =0@0I8<C C ?5@@V>@>4 203VB=>AB>B8 2V4AC4@0C5VB8 B0 @@0@<0@@5T ®

A;V4 70AB>A>2C20B8 C F59 ?5@V>4 BV;L:8 B>4V, :>;8 ?>B5=FV9=0 :>@8ABL 2V4 70AB>AC20==O
?5@528ICT <>6;8289 @878: 4;O ?;>40. V4><<, I> ?@>?0D5=>=C 3V4@@>E;>@@84 4>;0T ?;0F5=B0@@=89
10@T@ C ;N48=8. >2V4><<;O;>AO, I> :>=F5=B@0FVO ?@>?0D5=>==C C ?C?>28==V9 :@>2V AB0=>>28;0
30 % 9>3> :>=F5=B@0FVW C <0B5@@@8=AL:V9 :@>2V.
>A;V465=L I>4> 282G5==O 5:A:@5FVW ?@>?0D5=>==C 3V4@>E;>@84C C 3@@C4=4@5 <>;>:> ;N48=8 =5
?@>2>48;;>AO. 5O:V 40=V A2V4G0BL, I> ?@>?0D5=>==C <>65 ?@>>8:0B8 C 3@@C4=4@5 <>;>:>.
0B5@O<<, O:V 3>4CNBL 3@C44N, ?@>?0D5=>==C 3V4@@>E;>@84 A;V4 70AB>A>A>B8 7
>15@56=VABN.

*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.*
>B@@V1=> 2@@0E>2C20B8, I> C GCB;828E E2>@@@8E ?@@8 70AB>AC20==V ?@@5?0@@0BC <>6CBL
28=8:=CB8 ?>1VVG=V @50FVW (=5GVVB:VABL 7>@@C, 70?0<>@@>G5==O, A;01VABL, ?>ABC@@0;L=0
3V?>B5=7VO), O:V <>6CBL 2?;820B8 =0 H284:VABL @50:FVW ?0FV5=B0. B0 ?>?5@@5465=O
740B=VABL :5@C20B8 B@0=A?>@B=8< 70A>@10< 01> @>1>B0B8 7 C20305N =0 ?>B5=FV9=0 1V0B8 >1?V<8,
@>15AB, I> ?>B@51C5 ?@8=B5@@5F=VA :>=F5=B@0FVW C2038.

!?>AV1 70AB>A>>2C20==O B0 4>78.
"5@0?VN ® @5:><5=4>2C5BBLAO @>7?>G8=0B8 C 3@A?VB0;L=8E C<>20E, ?@@8 2?4:8 WW ?>28=5=
;V:0@@, O:89 <0T 4>A2V4 4;V:C20==O 04@>1V20==O 2 C<>20E :04@@5V>;@>3VG=>3>
A?@@AB56@565@=O, I> 2:;NG0T <>6;82VABL 2@>1;5==O :0@@4V0;L=>W 05A:C20==O B8A:C.
/:I> :> QRS ?>4>26CTBLAO 1V;LH =V6 =0 20 %, 4>7C A;V4 75<5=HC8B8 01> ?@8?8=8B8 ?@@89><
?@5?0@@0BC, 4>:8 ?>:07=88: =5 ?>25@=5BLAO C <56V =>@<8.
'5@57 3V4@:89 A<0: B0 ?>25@E=52C 0D50B=>ABL C 4VN ?@>?0D5=>==C B01;5B:8 A;V4 >2B0B8 FV;8<8
(=5 @>76@@>2CN8), 70?5820N>6N @V:8N>N.
0AB>A>>2C20==O 4>@>A;8< 2=CB@>28<8 @>7?@@CN, =0 ?>GG0B:C ;V:C20==O ?> 150 <3 3 @078 =0 4>1C,
71V;LHCN8 4>7C 7V 3V4>09<5=H5 B@0845==8< 2V4=5V5@@;20;><;>4N, 4> 300 <3 2 @078 =0 4>1C, 0 C @>7V
?>B@@518 4> <0:A8<0;L=>W 4>78 300 <3 3 @078 =0 4>1C. ;O ?@0FV=B2 2 V7 <0A>N BV;0 <5=H5 70 :3
@5:><5=4>2CTBLAO ?>G0B:>2C 4>7C <0:@@8<CV 4>78, V=42V4C0;L=>.
A>18 ;VB=L>3> 2V:C
V4 G0A ;V:C20==O ?@5?0@0B>< >1>6CV=> >1B56@565@=O ?@@8 :5@C20==V ?@@8AB56@@5@=O 1V7 >A>18=89 V=H8< :8@2CNGV :;V:C20==O ?@>>AC>B8B8 7 O>B@8<0==O> ?>B5=FV9=0 F8E >1?V=8 C
=56G8E 4>@@>E.
?>ABC@@0;L=0 3V?>B5=7VO 2 FV;8 ?>4>26CTBLAO 4>=2VN>4VN >1B56@@5@5B8 157?5FV 01>
5D5:B82=>5N>ABV, 0;5 75 <>65 28=8:=CB8 ?>B5@@5F=VA :0@@4V0;L=>W 45FV5=V5@V5@565F 8>A=89C2C4565, B@@56=0B8 ?5@@51C20N
?V4 @5B5;L=8< A?>AB56@6565==O78 ?>B@@51C> 74V9A=N20N20==8 G5@57 5-8 4=V ?>B5@@56565 V;V:C20==O.
>@0E5==O B0 DVABL@@C20==O =8@565: B0 >1?V=>>8 >1?V=>8
?>ABC@@0;L=0 3V?>B5=7VO V7 ?>@0E5==8 B0 DVAB@C20==8 =8>8@565: B0 >1?V=>8 <>65 A>8@565=565@@5=0 :C
:0@@4V0;L=>W 05D0@@=40@@>>0>0>8 05A5@F878FG>V5@5 4>7. ">

V;0:C20==O.
@5:><5=4>2C5 =5 70AB>A>>2C5B8 4@>1565@=O 4V1>

5@@54>7C20==O.
AV5@>4>>7C20==O ?@@8 70AB>A>>2C20==V
5VG0F<;LB0B0 2?;820CV 70B0C20==O ?@@8 70AB>A>>2C20==V ?@@0FV=B0 G5@57 5-8 @078 =0 4>1C C :V5@@5@0>B56=89C2C4565
?>B56@@@5=565==O<8 35=5@5 V;V:C20N2C4565>4N8 A>85@@5@565@=565@=565N2C4565=, B56565=56V565@@56=0B8 >1?V=>8 A?5:?56@@56=56=0 ?@@0565465@6565@56>65>?>6565@5656565 ?>B56@@@56565=4>65@565>065V>@@>65565
@@565565656565656565565..."

@07V BO6:>3> >B@CT==O <>6;8289 @>728B>: ::;>=V:>-B>=VG=8E AC4✕<, ?0@5AB57V9, A>=;82>ABV, :✕8 B0 7C?8=:8 48E0==O.

'5@57 28A>:89 ABC?V=L 72O7C20==O 7 1V;:0<8 :@>2V (>95 %) B0 25;8:89 >1T< @>7?>4V;C 35 <>4V0;;V7 T =55D5:B82=8<, A?@@>18 5;V

@V< 70AB>AC20==O 7030;L=8E =52V4:;04=8E 70E>4V2 ?>B@@@V1=> :>=B@>;;N20B8 >A=>2=V ?>:07=8:8 68BT4VO;L=>>ABV ?0FVT=B=B0 2 C<>20E 2V44V;5==O V=B5=A82>=W B5@@0?VW, 0 C @07V =5>1EV4==>ABV ?@@>2>48B8 WE :>@5:FVN.

D5:B82=8<8 70E>4=8 4;O :>=B@@>;;N @@8B3> B8A:C T 45DV1@8;OFVO B0 V=DC7VO 4>D0 ?@@>B5@@5>=;C. ;O ?>;53H5==O AC4✕< 70AB>A@>2NCNBL 2=CNBL@@8H=5==O 22545==O 4V075?0 >65 28=8:CB8 =5>1EV4==O?V4B@8<C20=B8=>=5 2V075?5@@>ABVOFVO 70B==;5 L O: <5E0=VG=0 25=B8;OFVO ;535=V2 B0 =5?@><89 <0A06 A5@FO.

09G0ABVH8<8 B0 =09?>H8@@5=VH8<8 ?>1VG=8<8 @50:FVNVVVV<8 @@@VW @5AF@>2V7=<>=5 ?@@>2070 T=8<;V ?>0D5>>=><<, T 70?0@<@>0G@5==O, @@@@CH5==O A5@F52>W ?@@>2V4==>>ABV B0 2V4GCBBO A5@F518BBO.

86G5 =02545=> ?>1VG=V @50:FVW @@@VW, I> A?>AB5@@53V30;8AO ?@8 =09<5=H<5 C >4=>3> 7 885 ?0FVT=BV2, O:V >B@@8B0>0D5>>=>>=><<C 3V4@@>E;>=;VW @0B4>=>=>>0B@0 C?>2V;L=5>=><<=V@@5:0 C ?0ABL>E :>;V;V5>=VG=8E 4>A;V4065==OE D078 B0 C 42>E :;V=V:=VG=8E 4>A;V4065==OE D078 . GV:CTBLAO, I> ?>1VG=V @50:FVW @@@VW B0 WE G0AB>BO C:070=V 403V4;8=V D@0 <=5309>3> 282V4;5==O 1C4CBL ?@4V1=8<8 B8. 86G5=>2545=V @@@@VW @50:FVW B0:>6 2:;NG0NBL ?@@>2V4>V 4>A;V4065=>W@@5:0, O: 282V4;5==O 1C4CBL ?@4V<>=>>B8. ?>1VG=V @50:FVW @@@VW, I>=09<5=H 9<>65 2V4@@=> ?>2V4>=>2V ?>1VG=V @50:FVW 4>A;V4065==O, =>2545=V@@5:0 70 A8AB5<0@V<8<=>=<5>GA< >@30=V2 V =0 G0AB>B0<8<=>=;5>@@5:0 B0 =8648 =5 28B8: 4C65: 4C65 @VV4:V (³ 1/10), @VV4:V> (³ 1/100 V < 1/10), =5@VV4:V> (³ 1/1000 V < 1/100), @VV4:V>B0 =55V4065 (?>1VG=V @50:FVW @@@VW 7 ?>1VG=@@0B0A@53>>=>2>3> 4>A;V4065=>W@@5:0; @V4:V>BV 287=0G8B8 =5>GC< >B@@B0>= 7 =0=<>=5 40=8E).

5G0AB>V> B@@>=1>78B>?5=VW; @V4:V>B0 =55V4065 03@0=C;;>>F8B>7, ;5A9>:>?5=VW, 3@0=C;;>>F8B>?5=VW, 0=5=V

5G0AB>V> 0;5@3VG=V @50:FVW, ?>7@8B8A82>89 B8B@@@ ANA; @V4:V>B0 =55V4065 3V?5@@@5:GCB;82VABL(I> <>65 ?@@>O2;OB8AO E;V5;5@@8@><, ?0BB>G8<><@53V5;8A@>7><, ?0BB<<=3VG=8AC 7

5G0AB>V> 7=865==O 0?5B8BC.

'0AB>V> B@@827>6=VABL, @V4:V>BV =55V4065 2=CBV A8AB5==O =8@@VW B0 =5>@@>C<@V B0 >@@8C<5>=>V

C65 G0AB>V> 70?@@0<>@@>G5==O (70 28=>:;@>2:>B 25@@B83>V4); @0AB>V> 3>;>2=89 18;L, 48A3527VV, 157A>@==O, A>=;82VABL; =5G0AB>V> A8=:>@@V, 0B0:AV>, ?0@5AB57VV,?>@G5==O <>2;5==O, 45?@@5AVVV, 2B@@0B0@>0E>>4== ?0B0V7=;VA8=8, HC< C 2CE0E, 2V4GCBBO =5728G09>3> 70?0EC; @V4:V>B0 =5@2V7=0 =5@2>2>ABL, 5:A@@>0G82>0

'0AB>V> =5GVVV:VABL 7>@C; =5G0AB>V> ?>4@>@>7=5==O >@C9.

5G0AB>V> 25@@B83>.

C65 G0AB>V> ?@@>@@>G5==O A5@F52>W ?@@>2V4==>ABV (2::NG0NG8 A8>=>0B@@>V>B;L=C, 0B@@>V>25=B@@>C;O@V>B===V B0 V=B@@0>=25=B@@>C;O@VV 1:>=>>04C), 2V4GCBBO A5@F518BBO; @V4:V>BV A8=5:CA>@20 1@@048:0@VVO, 1@@048:0@VVO, B0EV:0@VVO, 2V4GCBB=ABBVO ?5@@@1VVV, 71V;LH5==O B8A:C B0 =5@>@C A;CEC, ?5@@@54A5@FV0=5 7 A5@F52VANCN A5@F52>= C:@>O2;5==O =5@@>>C< V=B5@2>0;C, ?5@@@1V8L8=><8; =5G0AB>V> 5:AB@@0@@@C>V>VB>7:; @V4:V>B0 =55V4065 7C?8=:0 A5@FO. >A>1;82CC C203C A;V4 7@@=>@@C B8 =0 @>7782>:=0 AG0A88B>V>AB@0>>GA<0@@==N7>=>0B@@>B85 ?@@>0@@>B>V(torsades de pointes); @V4:V>B0 =55V4065 25=B@@>C;O@=0 1@@048:0@VVO, 75@@0B85;L=0 DV1@@8;OFVV, A5@F520 =5>ABBV0B>=VABL (<>65 ?@@8A8>=OB8AL 7 04C=>>A@@F52>W =5>ABBV0B>=VABL), 7C?8=:0 A5@FO @V4:>@@8C< A5@F528E A8=4@@>=V: @@@>@@VN >@@V<VN.

1>:C AC48=.

5G0AB> 0@B5@V0;L=0 3V?>B5=7VO; G0AB>B0 =52V4><0 >@B>AB0B8G=0 3V?>B5=7VO.

1>:C 48E0;L==>W A8AB5<B5<B5<8, >@30=V2 3@C4=>W :;VB:8 B0 A5@54>ABV==O.

'0AB> 48A?=>=>5.

1>:C H;C=:>:=:>2>-:8H:>2>3> B@0:BC.

'0AB> 1V;L C 682>BV, 1;N20==O, =C4>B0, 4V0@5O, 70?>@, ACEVABL C @>BV, ?>@CH5==O ;A0:C, 48A?5?AVO, 0=>@5:AVO; =5G0AB> 74CBBO 682>B0,<5B5>@87<, 30AB@@VB5=B8B; G0AB>B0 =52V4><0 ?>7828 4> 1;N20==O, H;C=:>2>-:8H:>2V ?>@CH5==O.

1>:C 35?0B0V1V;V0@=>W A8AB5<B5<8.

5G0AB> ?>@CH5==O DC=:FVW ?5GV=:8 (F59 B5@<V D>AD0B078 :@>2V); G0AB>B0 =52V4><0 35?0B>F5;N;O;@ C@065==O, E>;5AB07, 35?0B8B B0 6>2B0=8FO=8F0.

1>:C H:V@=8 B0 ?V4H:V@=>W :;VB:8=8.

5G0AB> :@>?82O=:0, A25@1V6, 28A8?0==O, ?@5G5@2==O H:V@8.

1>:C A:5;5B=>-<O7>2>W B0 A?>;CG=>W B:0=8=8 B0 :VAB:8.

'0AB> 1V;L C AC3;>10E, =5G0AB> <'O7>2V AC4><8, <'O7>20 A;01VABL;G0AB>B0 =52V4><0 ;N?CA?>4V1=89 A8=4@>< >7;048 @5?0@0FVW:B82V2==O A8AB5<8 B0 <>;N>7V=8E =0;V3?>;8 B0 7'O2: 70;878.

5G0AB> 5@5:FV;L;=0 48AD:=V; G0AB>B0 =52V4><0   7<5=H5==O :V;L:>ABV A?5@<0B>7>W428 A?5@<V (F5 O28I5 T >1@0B=5=8< ?@8 ?@8?8=5==V B5@0?VW ?@>?>D5=>>=5===).

1>:C A5G>282V4=>W A8AB5<8 B0 =8@>:.

5G0AB> =5D@>>B8B0 89 A8A4><8=E; 7 =52V4><>N G0AB>B>N =89@:>2>4@0 =54>AB0B=VABL.

030;L=V ?>@CH5==O.

'0AB> 1V;L C 3@C4=V9 :;VBFV, A;01VABL, 2B><0;N20==O, 30@OG:0, ?B4@287I5 0 ?VB;82VABL; =5G0AB> 0;>?5FVO; ?@428I5 @>==5 =>:>BV= 3;N:>78 :@>2V, 1V;L; G0AB>B0 =52V4><0 3V?>@=0B@V2<VN @@B@8VV @>7;048 A5:@5FVW .

"5@ABV. 3 @>:8.

#<>28 715@V30==O.

15@V30B8 C =54>AB0B=>ABV=>=>

#?0:>2:0.

"01;5B:8 ?> 150 <3: ?> 10 B01;5B>:: C 1;VAB5@V, 5 1;VAB5@V2 C :0@B>=>==V9 :>@>1FV.

"01;5B:8 ?> 300 <3: ?> 10 B01;5B>:: C 1;VAB5@V, 5 1;VAB5@V2 C :0@B>=>==V9 :>@>1FV.

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

0 @5F5?B><

8@>1=8:.

..&! @030 0.B. /

PRO.MED.CS Prah0 a.s.

VAF5?=0E>465==O 28@>1=8:0 B0 04@5A0 <VAF5==O 9>3> 4VO;L=>ABV.

"5;>GA:0 1, 140 00 @030 4, '5AL:0 5A?C1;V:0 /

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