

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

%
(VERAPAMIL HYDROCHLORIDE)

!,:04:

4VNG0 @5G>28=0: 25@0?0E;>@84;
1 B01;5B:0 E;>@84C C ?5@5@0EC20==V =0 100 % ACEC @5G>28=C;
4>?>28=8: :@>E<0;L :C:C@C47O=89, ;0:B>78 <=>3V4@0B, :>?>2V4>=, <03=VN AB50@0B.
;V2:>CB2>@NNG5 ?>:@8BBO: 3V4@>:A8?@>V;<5B8;F5;N;>70, ;0:B>78 <=>3V4@0B, B8B0=C
4V>:A84
(171), ?>;V5B8;5=3;V:>;L, B@80F5B8=.

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N.
A=>2=V DV78:>-EVABV: :@C3;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 1V;>3> :>;L>@C, 7
42>>?C;>;N ?>25@E=5N. 0 ?>?5@5G=>W AB@C:BC@8.

\$0@<0:>B5@0?52B8G=0 3@C?0. !5;5:B82=V 0=B03>=VAB8 :0;LFVN 7 ?5@5206=>N 4VTN =0 A5@F5.
>EV4=V D5=V;0;:V;0>4 "% C08D A01.

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

\$0@<0:>48=0
5@0?0E;>@84 T A5;5:B82=8< 1;>:0B>@< :0;LFVT28E :0=0;V2 L B8?C I :;0AC, G8=8BL
0=B80=3V=0;L=C B0 3V?>B5=782=C 4VW. ;>:CT ?>B5=V0;70;56=V :0;LFVT2V :0=0;8 B0 ?>@CHCT
=04E>465==O V>=V2 :0;LFVN 2A5@548=C ;:VB8=, 7>:@5<0 :0@4V>F8BV2 B0 ;:VB8= 3;045=L:8E
<07V2 AC48=, :=F5=B@0FVO :0;LFVN C :@>2V ?@8 FL>
=B80=3V=0;L=0 4VO ?@5?0@0BC @50;V7CTBLAO 70240:8 7=865==N B>=CAC :>@>=0@=8E B0
?5@8D5@8G=8E 0@B5@V0;L=8E AC48=, ?>;V?H5==N :@>2?>AB0G0==O A5@F52>3><O70, C B>
20=8E 4V;O=:0E; 7=86CT ?>B@51C:0@40 2 :8A=V, 7<5=HCNG8 A:>@>B;82VABL:0@40 B0
71V;LHCNG8 :>@>=0@=89 :@>2>BV:. =B80=3V=0;L=89 5D5:B 7C<>2;5=89 B0:>6 207>48;0BCNG>N
?5@8D5@8G=>N 4VTN, I> ?@872>48BL 4> 7<5=H5==O ?>AB=020=B065==O V ?>B@518 :0@40 2 :8A=V.
5@0?0E;>@84 =0;568BL 4> 0=B80@8BIV ;:0AC. =B80@8B25=B@8:C;O@=> ?@872>48BL 4>
C?>2V;L=5==O 02B<0B872>3> 2C7;0, 5:B>?VG=8E 2>3=8I C ?5@54A5@4OE V H284:>ABV
?@>2545==O 71C465==O G5@57 0B@V>25=B@8:C;O@=89 2C7>;. =0A;V4>: FL>3> ?>4>26CTBLAO
5D5:B82=89 @5D@0:B5@=89 ?5@V>4 C A8=CA>2> B0 0B@V>25=B@8:C;O@=>2V;L=NTBLAO
A8=CA>289 @8B<, 7<5=HCTBLAO G0AB>B0 A5@F528E A:>@>G5=L.
=B83V?5@B5=782=0 4VO 25@0?0E;>@84C 7C<>2;5=0 @>7A;01;5==O< 3;045=L:8E <07V2 AC48=,
7=865==O< 7030;L=>3> ?5@8D5@8G=>3> AC48==>3> >?>@C, 0@B5@V0;L=>3> B8A:C, O: ?@028;>;,
157 @>728B:C ?>ABC@0;L=>W 3V?>B5=7VW B0 @5D;5:B>@=>W B0EV:0@4VW; 1@048:0@4VO
(G0AB>B0 A5@F528E A:>@>G5=L<5=H5 50 70 E28;8=C) @>72820TBLAO @V4:>.

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

VA;O ?5@>@0;L=>3> ?@89> 2 B>=:> 2A<>:BCTBLAO ?>=04 90 % 22545=>W 4>78 25@0?0E;>@84C.
@5?0@0B <5B01>;V7CTBLAO ?5@5206=> 2 ?5GV=FV 2=0A;V4>: V=B5=A82=>3> <5B01>;V7E>465==V
:@V7L 2>@VB=C A8AB54>ABC?=VABL ?@5?0@0BC AB0=>28BL 20-35%. 0:A8<0;L=0 :=F5=B@0FVO
25@0?0E;>@84C 2 ?;072V 2V47=0G0TBLAO G5@57 1-2 3>48=8 ?VA;O ?@89>
!BC?V=L 7=865==O B8A:C :@>2V =5 70;568BL 2V4 :=F5=B@0FVW 5@0?0 3V4@>E;>@84C 2 ?;072V.
1V;>0<8 :@>2V 7207CTBLAO ?@81;87=> 90 % ?@5?0@0BC.
5@0?0E;>@84 ?@>=8:0T :@V7L ?;0F5=BC B0 5:A:@5BCTBLAO 2 3@C4=5 <>;>:. !5@54=V9 ?5@V>4
=0?V2282545==O AB0=>28BL 2,8-7,4 3>48=8 ?VA;O?5@H>3> ?@89> 4,5-12 3>48= =0 B;V B@820;>3>
?@89>W 2V:>2>W 3@C?8 ?5@V>4 =0?V2282545==O <>65 71V;LHC20B8AL.
5I>402=> >45@60=V 40=V A2V4G0BL, I> =5<0T @V7=8FV C D0@<0:>:V=5B8FV 25@0?0@>28<8 =8@:0
<8 B0 C ?0FVT=V2 7 B5@N AB04VTN =8@:>2>W =54>AB0B=>ABV.

?0FVT=BV2 7 ?5GV=>2>N =54>AB0B=VABN ?5@V>4 =0?V2282545==O 71V;LHCTBLAO 4> 14-16
3>48=, >1T< @>?>4V;C 71V;LHCTBLAO, ?;07<>289 ;;V@5=A AB0=>28BL ?@81;87=> 30 % =>@<8. ">
7C 4;O B0:8E ?0FVT=BV2 7<5=HCNBL 4> 1/3 728G09=>W 4>1>2>W 4>78. @5?0@0B 282>48BLAO
?5@5206=> =8@:0<8
(70 %), G0AB:>2> :8H5G=8:>

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

>:070==O.

- @B5@V0;L=0 3V?5@B5=7VO.
- □H5@>10 A5@FO, 2;:NG0NG8 AB01V;L=C AB5=>:0@4VN =0?@C65==Q =5AB01V;L=C
AB5=>:0@4VN (?@>3@5ACNG0 AB5=>:0@4VO, AB5=>:0@4VO A?>:>N) 207>A?0AB8G=C
AB5=>:0@4VN (20@V0=B=0 AB5=>:0@4VO, AB5=>:0@4VO @8=F<5B0;0), ?>ABV=D0@:B=C
AB5=>:0@4VN C ?0FVT=BV2 157 A5@F52>W =54>AB0B=>ABV, O:I> =5 ?>:070=V□-
04@5=>1;:>:0B>@8.
- □@8B:A87<0;L=0 =04H;C=>G:>20 B0EV:0@4VO, <5@5EBV==O/B@V?>BV==O ?5@54A5@4L 7V
H284:>N 0B@V>25=B@8:C;O@=>N ?@>2V4=VABN (70 28=OB:>< A8=4@>>;LD0-0@:V=A>=0-#09B0
WPW).

@>B8?>:070==O.

- V?5@GCB;82VABL 4> 25@0?04> V=H8E :>=5=BV2 ?@5?0@0BC.
- 0@4V>35==89 H>:.
- >AB@0 D070 V=D0@:BC :0@40 7 CA::;04=5==O<8 (1@048:0@4VO < 50 C4/E2, 0@B5@V0;L=0
3V?>B5=7VO (A8AB>;VG=89 B8A: =86G5 90 << @B. AB.), =54>AB0B=VABL ;V2>3> H;C=>G:0).
- "06:V ?>@CH5==O ?@>2V4=>ABV: A8=>0B@V0;L=0 B0 0B@V>25=B@8:C;O@=0 (V) 1;:>:040 II-III
ABC?5=O (70 28=OB:>< ?0FVT=BV2 7V HBCG=8< 2>4VT< @8B
- !8=4@>< A;01:>ABV A8=CA>2>3> 2C7;0 (70 28=OB:>< ?0FVT=BV2 7V HBCG=8< 2>4VT< @8B
- !5@F520 =54>AB0B=VABL 7V 7=865==O< D@0:FVW 28:84C <5=H5 35 % B0/01> B8A:>< C
;535=52V9 0@B5@VW 28I5 20 << @B. AB. (O:I> BV;L:8 2B>@8==0 =04H;C=>G:>20 B0EV:0@4VO =5
?V440TBLAO 2?;82C B5@0?VW 25@0?0<).
- 5@5EBV==O/B@V?>BV==O ?5@54A5@4L ?@8 =0O2=>ABV 4>40B:>28E ?@>2V4=8E H;OEV2 (=0
B;V A8=4@># B0:8E ?0FVT=BV2 ?@8 70AB>AC20==V 25@0?0E;>@84C T @878: @>728B:C
H;C=>G:>2>W B0EV0@8BG:>2C DV1@8;OFVN.
- 4=>G0A=5 70AB>A>2C20==O 1;:>:0B>@V2 □-04@5=>@5F5?B>@V2 4;O 2=CB@VH=L>25==>3>
22545==O (70 28=OB:>< V=B5=A82=>W B5@0?VW).

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

□-04@5=>1;:>:0B>@0<8: 71V;LHCT 270T<=C ?@83=VGC20;L=C 4VN =0 02B<<0B87<
A8=>0B@V0;L=>3> 2C7;0, V-?@>2V4=VABL V A:>@>B;82VABL:0@40, 2=0A;V4>: FL>3>
?V428ICTBLAO @878: @>728B:C 28@065=>W 0@B5@V0;L=>W 3V?>B5=7VW, V- B0 S-1;:>:04,
1@048:0@4VW, A5@F52>W =54>AB0B=>ABV, >A>1;82> ?@8 70AB>AC20==V 28A>:8E 4>7□-
04@5=>1;:>:0B>@V2 01> ?@8 WE 2=CB@VH=L>25==>
A>1;82C 3@C?C @878:C AB0=>2;OBL ?0FVT=B8 7 >7=0:0<8 E@>=VG=>W A5@F52>W
=54>AB0B=>ABV, 28@065=>W :0@4V?>0BVW 01> BV, O:V =5402=> ?5@5=5A;8 V=D0@:B:0@40. □>
<1V=>20=C B5@0?VN 5@0?0C 3V4@>E;>@84C 7 □-04@5=>1;:>:0B>@0<8 A;V4 ?@>2>48B8 BV;L:8 70
GVB:8<8 ?>:070==O<8 B0 ?V4 AC2>@8< :>=B@>;5< ;V:0@O.
0=B83V?5@B5=782=8<8 ?@5?0@0B0<8 (=0?@8:;04, 207>48;0B0B>@8, V=3V1VB>@8 ,
4VC@5B8:8,
α-1;:>:0B>@8, ?@07>78= B0 B5@07>78=): 25@0?0E;>@84 ?>B5=RVNT WE 4VN.
B@8F8.;VG=8<8 0=B845?@5A0=B0<8, =59@>;5?B8:0<8: ?>B5=RVN20==O 3V?>B5=782=>W 4VW
25@0?0E;>@84C.
A5@F528<8 3;V:>7840<8 (=0?@8:;04, 483>:A8=><): A;V4 2@0E>2C20B8, I> =0 ?>G0B:C
;V:C20==O
(1-9 B8645=L) @V25=L 483>:A8=C C A8@>20BFV :@>2V ?V428ICTBLAO =0 50-70 %, B>B@V1=>
2V4:>@83C20B8 4>7C 483>:A8=C, 0 9>3> @V25=L C A8@>20BFV :@>2V ?5@V>48G=> :>=B@>;N20B8,
>A>1;82> =0 ?>G0B:C ;V:C20==O.

0=B80@8B ?@5?0@0B0<8 -III ;:0AC (2 B>40@>=><): =5 @5:><5=4CTBLAO >4=>G0A=5
70AB>AC20==O.
487>?V@0< (@8B<): =5 A;V4 70AB>A>2C20B8 >4=>G0A=>, ?@89<< 487>?V@048= 4> ?>G0B:C
70AB>AC20==O 25@0?0E;>@84C, B0 <>6;82? ?>=>28B8=5 @0=VH5 =V6 G5@57 24 3>48=8 ?VA;O
?@8?8=5==O ?@89>E;>@84C.
D;5:0W=V4> VAB>B=> 7:0@4, A?>2V;L=NTBLAO 0B@V>25=B@8:C;O@=0 ?@>2V4=VABL B0
71V;LHCTBLAO B@820;VABL @5?>;O@870FVW.
EV=V4V=><: 7<5=H5==O ;:V@5=AC EV=V48=C (~ 35 %) ?@8 ?5@>@0;L=>6;8289 @>728B>:
0@B5@V0;L=>W 3V?>B5=7VW, 0 C ?0FVT=BV2 7 3V?5@B@>DVG=>N >1AB@C:B82=>N :0@4V>
?0BVTN =01@O: ;535=V2. ">18420 ?@5?0@0B8 @07>
?5@>@0;L=8<8 ?@>B870?;V4=8<8 ?@5?0@0B0<8, 3V40=B>W=><, A0;VF8;0B0<8, AC;LD0=V;0
2=0A;V4>: 28A>:>3> ABC?5=O 7207C20==O 25@0?0
A>;O<8 :0;LFFVN B0 2VB0< D: D0@<0>;>3VG=89 5D5:B 25@0?0E;>@84C, 9<>2V@=>, 7<5=HCTBLAO.
?@>?@0=>;>;><, <5B>?@>;>;> 25@0?0E;>@84 <>65 7=86C20B8 WE=V9 ;:V@5=A.
@8D0><, D5=>10@1VB0;> <>6CBL 7=86C20B8 5D5:B82=VABL ?@5?0@0BC O: V=4C:B>@8A>
<0;L=8E D5@<5=BV2.
A>;O<8 ;:VBVN, B5>DV;V=> ?V4 4VTN 25@0?0=F5=B@0FVO C A8@>20BFV :@>2V <>65 7O, B> ?@89
<0NBL FV ?@5?0@0B8, ?>28==V 1CB8 ?V4 @5B5;L=8<=03;O4>
F8;>A?>@8=><, 525@>;V<, A8@>;V<, B0:@>;V<, V=3V1VB>@0<8 A5@>B>=V=>28E
@5F5?B>@V2 (B0:8< O: 0;<>B@8?B0=), :0@10<075?V=>< B0 B5>DV;V=> 25@0?048BL 4>
?V428I5==O WE @V2=O C A8@>20BFV :@>2V ?@8 >4=>G0A=>AC20==V.
:>;EVF8=> 25@0?0?V428I5==O 9>3> 4VW.><1V=>20=5 70AB>AC20==O F8E ?@5?0@0BV2 =5 @5:>
<5=4CTBLAO.
0=B03>=VAB0<8 H2-@5F5?B>@V2, F8<5B848=> <>6;825 ?V428I5==O :=F5=B@0FVW 25@0?02V.
0=B8@5B@>2V@CA=8<8 ?@5?0@0B0<8 (B0:8<8 O: @8B>=02V@, V=48=02V@): <>6;825 ?V428I5==O
:=F5=B@0FVW 25@0?02V. ">@8AB>2C20B8 5@0?0E;>@84 ?@8 FV9 :=<1V=0FVW A;V4 7
>15@56=VABN 01> 9>3> 4>70<0T 1CB8 7=865=0.
V=3V1VB>@0<8 ->-@54C:B078 (A8<20AB0B8=, 0B>@20AB0B8=, ;>20AB0B8=);:V:C20==O AB0B8=0<8
A;V4 @>?>G8=0B8 7 =09=86G8E <>6;828E 4>7 B0 ?>ABC?>2> WE 71V;LHC20B8. /:I> ?0FVT=BC, O:89
265 ?@89<0T 25@0?01EV4=5 ?@87=0G5==O AB0B8=V2, A;V4 2@0EC20B8 =5>1EV4=5 7=865==O WE
4>78 V ?V4V1@0B8 4>7C20==O 2V4?>2V4=> 4> :=F5=B@0FVW E>;5AB5@8=C C ?;072V.
A8<20AB0B8=>< (C 25;8:8E 4>70E): ?V428ICTBLAO @878: ?0BVW, @014>;V7C. >7C20==O A8
<20AB0B8=C <0T 1CB8 2V4?>2V4=> C73>465=8
D;C20AB0B8=><, ?@020AB0B8=>< V @>7C20AB0B8=> 2>=8 =5 <5B01>;V7CNBLAO A8AB5<>N CYP3
A4 V 2 7207:C 7 F8< ?@0:B8G=>=5 270T<>4VNBL 7 25@0?0
ACIAB@0B0<8 F8B>E@>5=78, =0?@8;:04, V=3V1VB>@0<8 !SE (2 B.G. ;>20AB0B8=, A8<20AB0B8=,
0B>@20AB0B8=): <>6;825 ?V428I5==O @V2=O F8E ;V:0@AL:8E 70A>1V2 C ?;072V, I> ?V428ICT @878:
B>:A8G=>3> C@065==O <07V2.
V=30;OFV9=8<8 0=5AB5B8:0<8 01> 7 1;>:0B>@0<8 =59@><07>2>W ?5@540GV: 4>78 ?@5?0@0BV2
A;V4 2V4:>@83C20B8, I>1 C=8:=CB8 ?@83=VGC20;L=>W 4VW =0 A5@F52C 4VO;L=VABL.
@5:0:A0=B0<8: ?>B5=VNT WE=N 4VN.
<0:@>;V40<8 (=0?@8;:04, 5@8B@> ;:0@8B@> G5@57 270T<=89 2?;82 ?V428ICTBLAO @V25=L
25@0?02V.
0=B84V015B8G=8<8 ?@5?0@0B0<8 (3;VIC@84): ?V428ICTBLAO !<0E 3;VIC@84C =0 28 %.
4>:A>@C1VF8=>< (?5@>@0;L=>): ?V428ICTBLAO 1V>4>ABC?=VABL B0<0:A8<0;L=89 @V25=L
4>:A>@C1VF8=C 2 ?;072V C ?0FVT=BV2 7 4@V1=>;:VB8==8< @0:>< ;535=V2.
?@5?0@0B0<8 72V@>I>O ?@>4V@02;5=>3>: 7<5=HCTBLAO ?;>I0 ?V4 :@82>N :=F5=B@0FVO-
G0A, 71V;LHCTBLAO !<0E.
@5=B35=>:=B@0AB=8<8 70A>10<8: <>6;825 ?>B5=VNT20==O ?@83=VGC20;L=>3> 2?;82C 25@0?0
<0B87< A8=>0B@V0;L=>3> 2C7;0, V-?@>2V4=VABL V A:>@>B;82VABL:0@40.
5B0=>;> 25@0?07?04 B0 ?V428ICT 9>3> @V25=L 2 ?;072V, B8< A0<8< ?>A8;NTBLAO 4VO 5B0=>;C.
3@59?D@CB>28< A>:>?V428ICTBLAO 1V>4>ABC?=VABL 25@0?0
AC;LDV=?V@07>=> ?V428I5==O ;:V@5=AC ?5@>@0;L=>3> 25@0?04>ABC?=>ABV =0 60 %. >6;825
7=865==O 3V?>B5=782=>3> 5D5:BC.
0F5B8;A0;VF8;>2>N :8A;>B>N: ?V428I5==O @878:C :@>2>B5G.

483VB>:A8=><: 7<5=H5==O ;V@5=AC 483VB>:A8=C (≈ 27 %) B0 5:AB@0@5=0;L=>3> ;V@5=AC (≈ 29 %).

ICA?V@>=> 71V;LH5==O AUC B0 !<0E C 3-4 @078.

V><: 71V;LH5==O AUC (≈ 15 %) V

;0<> 71V;LH5==O AUC C 3 @078 B0 !<0E C 2 @078.

>A;V465==O <5B01>;V7E;>@84C in vitro?:070;8, I> 2V= <5B01>;V7CTBLAO F8B>E@><< 450

CYP3A4, CYP1A2, CYP2C8, CYP2C9 B0 CYP2!18. 5@0?0@>< D5@<5=BV2 CYP3A4 B0

-3;V:>?@>B5W=V2 (-gp). >2V4<;O;>AO ?@> ;V=VG=> 206;82V 270T<>4VW 7 V=3V1VB>@0<8

CYP3A4, I> AC?@>2>46C20;8AO ?V428I5==O< @V2=O 25@0?02V, B>4V O: V=4C:B>@8 CYP3A4

A?@8G8=O;8 7=865==O ?;07<>28E @V2=V2 25@0?0E;>@84C, B>1EV4=> ?@>2>48B8 <=VB>@8=3

I>4> 270T<>4VW 7 V=H8<8 ;V:0@AL:8<8 70A>10<8.

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

@5?0@0B A;V4 70AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0< 7 3>AB@8< V=D0@:B>< :0@40,

CA:;04=5=8< 1@048:0@4VTN, 28@065=>N 0@B5@V0;L=>N 3V?>B5=7VTN 01> 48ADC=:FVTN ;V2>3> H;C=>G:0.

5@0?0E;>@84 2?;820T =0 0B@V>25=B@8:C;O@=89 B0 A8=>0B@V0;L=89 2C7;8 B0 ?@>;>=3CT G0A

0B@V>25=B@8:C;O@=>W ?@>2V4=>ABV. 0AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0< 7 AV-

1;>:04>N I ABC?5=O, G5@57 <>6;8289 @>728B>: 0B@V>25=B@8:C;O@=>W 1;>:048 01> ABC?5=O 01>

>4=>?CG:>2>W, 42>?CG:>2>W 01> B@8?CG:>2>W 1;>:048 =V6:8 VA0, I> ?>B@51CT 2V4 25@0?0

E;>@84C B0 ?@87=0G5==O 2V4?>2V4=>W B5@0?VW 2 @07V ?>B@518.

5@0?0E;>@84 2?;820T =0 0B@V>25=B@8:C;O@=89 B0 A8=>0B@V0;L=89 2C7;8 B0 V=:;>8 <>65

A?@>2>:C20B8 28=8=:5==O 0B@V>25=B@8:C;O@=>W 1;>:048 01> ABC?5=O, 1@048:0@4VW,

0A8AB>;VW. V;LH 2V@>3V4=>, I> B0:V A8<8 1C4CBL A?>AB5@V30B8AO C ?0FVT=BV2 V7 A8=4@>

<< A;01:>ABV A8=CA>2>3> 2C7;0 (A8=>0B@V0;L=0 2C7;>20 E2>@>10), I> G0ABVH5

7CAB@VG0TBLAO C ?0FVT=BV2 ;VB=L>3> 2V:C.

A8AB>;VO C ?0FVT=BV2, O:V =5 <0NBL A8=4@>ABV A8=CA>2>3> 2C7;0, 70728G09 :>@>B>B@820;0

(:V;L:0 A5:C=4 01><5=H5), 7V A?>=B0==8< ?>25@=5==O< 4> 0B@V>25=B@8:C;O@=>3> 01> =>@

<0;L=>3> A8=CA>2>3> @8B F5 O28I5 =5 H284:>?;8==5, A;V4 =5309=> @>7?>G0B8 2V4?>2V4=C

B5@0?VN (482. @>74V; «>1VG=V @50:FVW»).

=B80@8B18, □-04@5=>1;>:0B>@8. 70T<=5 ?>A8;5==O :0@4V>20A:C;O@=>W 4VW (?V428I5==O

ABC?5=O 0B@V>25=B@8:C;O@=>W 1;>:048 28A>:>3> ABC?5=O, 7=0G=5 7=865==O G0AB>B8

A5@F528E A:>@>G5=L, ?>O20 A5@F52>W =54>AB0B=>ABV, 7=0G=5 7=865==O 0@B5@V0;L=>3>

B8A:C). !8<0B8G=0 1@048:0@4VO (36 C4/E2) 7 1;C:0NG8< 2>4VT< @8BAB5@V30;0AO C ?0FVT=BV2,

O:V >B@8G=8<8 :@0?;O<8 7 B8<>;>;< (□-04@5=>1;>:0B>@) =0 B;V ;V:C20==O 25@0?0E;>@84>

@8 >4=>G0A=>AC20==V 25@0?0:A8=>< A;V4 7<5=H8B8 4>7C 483>:A8=C (482. @>74V; «70T<>4VO 7

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

5@54 ?>G0B:>< ;V:C20==O 25@0?0< =5>1EV4=> :>AB0B=VABL C ?0FVT=BV2 V7 D@0:FVTN 28:84C

1V;LH5 35 % B0 045:20B=> :=B@>;N20B8 WE AB0= ?@>BO3< CAL>3> ?5@V>4C ;V:C20==O.

5@0?0E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN ?@8 =0O2=>ABV70E2>@N20=L 7 ?>@CH5==O

<8 =5@2>2>-<O7>2>W ?@>2V4=>ABV ?0FVT=B0< 7: Myasthenia gravis, A8=4@>>< 0<15@B0-B>=0,

?@>3@5ACNG>N <□O7>2>N 48AB@>DVTN NH5=0.

>15@56=VABN A;V4 ?@87=0G0B8 5@0?0E;>@84 ?0FVT=B0< 7 ?>@CH5==O< DC=:FVW ?5GV=:8 (@5:>

<5=4CTBLAO 7<5=H8B8 4>7C 4> 30 % 2V4 728G09=>W 4>1>2>W); 7 =8@:>2>N =54>AB0B=VABN (

@5B5;L=> :=B@>;N20B8 B@820;VABL Q-V=B5@20;C, 0 B0:>6V=HV >7=0:8 <>6;82>3>

?5@54>7C20==O 25@0?0E;>@84C).

!;V4 :=B@>;N20B8 B@820;VABL Q-V=B5@20;C =0 , 0B0:>6 V=HV >7=0:8 <>6;82>3> ?5@54>7C20==O

5@0?0E;>@84C C ?0FVT=BV2 (@53C;O@=89 :=B@>;L ", !!).

@8 ?@87=0G5==V 5@0?0E;>@84C A;V4 2@0E>2C20B8, I> >A>18 ;VB=L>3> 2V:C <>6CBL <0B8

?V428I5=C GCB;82VABL 4> 4VW ?@5?0@0BC, =02VBL 70 C<>2 728G09=>3> 4>7C20==O.

@5?0@0B 7C, B>3> =5 A;V4 70AB>A>2C20B8 ?0FVT=B0< V7 @V4:VA=8<8 A?04:>28<8 D>@<0<8

=5?5@5=>A8<>ABV 30;0:B>78, =54>AB0B=VABN ;0:B078 01> A8=4@>>< 3;N:>7>-30;0:B>7=>W

<0;L01A>@1FVW.

0AB>AC20==O C ?5@V>4 203VB=>ABV B0 3>4C20==O 3@C44N.

'VB:V B0 4>1@5 282G5=V 40=V 70AB>AC20==O ?@5?0@0BC 203VB=8< 6V=:0< 2V4ACB=V.">
?@5?0@0B A;V4 70AB>A>2C20B8 ?V4 G0A 203VB=>ABV BV;L:8 2 @07V=5>1EV4=>ABV.
5@0?0=8:0T G5@57 ?;0F5=BC B0 287=0G0TBLAO C ?C?>28==V9 :@>2V.
5@0?03> <5B01>;VB8 ?@>=8:0NBL C 3@C4=5 <>;>.: >70 25@0?0?040T 2 >@30=V7<
=>2>=0@>465=>3>, T =87L:>N (0,1-1 % 4>78, ?@89=OB>W <0BV@N), B>AC20==O 25@0?0
2060NG8 =0 @878: ?>O28 A5@9>7=8E ?>1VG=8E @50:FV9 C =>2>=0@>465=8E, O:V 7=0E>4OBLAO =0
3@C4=>4>2C20==V, 25@0?04 3>4C20==O 3@C44N <>6=0 70AB>A>2C20B8 BV;L:8 C @07V =030;L=>W
?>B@518 4;O <0B5@V.

40B=VABL ??;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> V=H8<8
<5E0=V7<0<8.

'5@57 0=B83V?5@B5=782=89 5D5:B 25@0?0E;>@84C, 70;56=> 2V4 V=482V4C0;L=>W @50:FVW,
740B=VABL :5@C20B8 B@0=A?>@B=8<8 70A>10<8, V=H8<8 <5E0=V7<0<8 01> ?@0FN20B8 2
=5157?5G=8E C<>20E <>65 1CB8 ?>@CH5=0. A>1;82> F5 AB>ACTBLAO ?>G0B:>2>W D078 ;V:C20==O,
?@8 ?V428I5==V 4>78, ?@8 7B5=782=>3> ?@5?0@0BC, 0 B0:>6 ?@8 >4=>G0A=>70AB>AC20==V
?@5?0@0BC 7 0;>3>;52V B0 C?>2V;L=N20B8 9>3> 282545==O, B>3>;N <>65 ?>A8;N20B8AO.

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

>78 ?V418@0B8 V=482V4C0;L=> 4;O :>6=>3> ?0FVT=B0.

"01;5B:8 :>2B0B8 FV;8<8, =5 @>7A<>:BC20B8, =5 @>76>2C20B8, =5 ?>4@V1=N20B8, =5 4V;8B8 =0
G0AB8=8; 70?820B8 4>AB0B=L>N :V;L:VABN @V48=8 (=0?@8:;04, 1 A;;O=:0 2>48, C 6>4=>289 AV:),
:@0I5 70 2A5 ?V4 G0A 01> >4@07C ?VA;O W48

>@>A;V B0 ?V4;VB:8 7 <0A>N BV;0 1V;LH5 50 :3

H5@>10 A5@FO, ?0@>:A87<0;L=0 =04H;C=>G:>20 B0EV:0@4VO, B@V?>BV==O/<5@5EBV==O
?5@54A5@4L

5:>5=4>20=0 4>70 AB0=>28BL 120-480 <3, @>7?>4V;5=0 =0 3-4 ?@89><8. 0:A8<0;L=0 4>1>20 4>70
?@5?0@0BC 480 <3.

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

5:>5=4>20=0 4>1>20 4>70 AB0=>28BL 120-360 <3, @>7?>4V;5=0 =0 3 ?@89><8.

!BV9:89 0=B83V?5@B5=782=89 5D5:B @>72820TBLAO ?@>BO3>< B86=O 2V4 ?>G0B:C B5@0?VW.

@8 AB5=>:0@4VW B0 0@8B 728G09=0 4>70 ?@5?0@0BC AB0=>28BL 80 <3 3-4 @078 =0
4>1C

(240-320 <3).

0:A8<0;L=89 5D5:B @>72820TBLAO, O: ?@028;>, ?@>BO3>< 48 3>48= 2V4 ?>G0B:C ;V:C20==O.

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

>ABC?=V 40=V >?8A0=> 2 @>74V;V «A>1;82>ABV 70AB>AC20==O». 0FVT=B0< 7 =8@:>2>N

=54>AB0B=VABN 25@0?0E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN B0 ?V4 @5B5;L=8< =03;O4>
>@CH5==O DC=:FVW ?5GV=:8

?0FVT=BV2 7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 70;56=> 2V4 ABC?5=O BO6:>ABV 4VO 25@0?0

E;>@84C ?>A8;NTBLAO B0 ?>4>26CTBLAO G5@57 C?>2V;L=5==O @>7?04C ;V:0@AL:>3> 70A>1C.">

7C20==O A;V4 2AB0=>2;N20B8 7 >A>1;82>N >15@56=VABN B0 @>7?>G8=0B8 7<0;8E 4>7 (=0?@8:;04,
4;O ?0FVT=BV2 7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 A?>G0B:C 2-3 @078 =0 4>1C ?> 40 <3, 2V4?>2V4=>

80-120 <3 =0 4>1C), 482. «A>1;82>ABV 70AB>AC20==O».

0 =5>1EV4=VABN ?>G0B:>2C 4>7C ?>ABC?>2> ?V428IC20B8 70;56=> 2V4 AB0=C ?0FVT=B0 B0

::V=VG=>W 2V4?>2V4V, O:0 >FV=NTBLAO ?V4 G0A 70AB>AC20==O ?@5?0@0BC.

*@8 =5>1EV4=>ABV 70AB>AC20==O 25@0?0 2 4>7V 40 <3 A;V4 70AB>A>2C20B8 ?@5?0@0B 7

<>6;82VABN B0:>3> 4>7C20==O.

5 ?@89<0B8 ?@5?0@0B C ?>;>65==V ;560G8.

5@0?0E;>@84 =5 <>6=0 ?@87=0G0B8 ?0FVT=B0< 7 V=D0@:B<< :0@40 ?@>BO3>< 7 4=V2 ?VA;O

?>4VW.

VA;O B@820;>W B5@0?VW ?@5?0@0B A;V4 2V4ABC?>2> 7=86CNG8 4>7C.

"@820;VABL ;V:C20==O 287=0G0T ;V:0@ V=482V4C0;L=>, 2>=0 70;568BL 2V4 AB0=C ?0FVT=B0 B0

?5@51V3C 70E2>@N20==O.

VB8.

VBO< ?@5?0@0B C 40=V9 ;V:0@AL:V9 D>@

5@54>7C20==O.

!8<8, I> A?>AB5@V30NBLAO ?@8 ?5@54>7C20==V 25@0?0ABV ?@89=OB>3> ?@5?0@0BC, G0AC, :>;8 1C;8 268BV 45B>;A8:0FV9=V 70E>48, B0 2V:C ?0FVT=B0.

!8<8: 0@B5@V0;L=0 3V?>B5=7VO, 1@048:0@4VO 4> 0B@V>25=B@8:C;O@=>W 1;>:048 28A>:>3> ABC?5=O B0 7C?8=:8 A8=CA>2>3> 2C7;0, 3V?5@3;V:5@ B0 <5B01>;VG=89 0F84>7. !?>AB5@V30;8AO ;5B0;L=V 28?04:8 2 @57C;LB0BV ?5@54>7C20==O.

V:C20==O: ?>28==> 1CB8 3>;>2=8< G8=>< ?V4B@8β-04@5=5@3VG=C AB8 2=CB@VH=L>25==5 22545==O ?@5?0@0BV2 :0;L:FN (:;L:FN E;>@84) 5D5:B82=> 70AB>A>2CNBL 4;O CAC=5==O A8 7C20==O ?@8 ?5@>@0;L=>AC20==V 25@0?0E;>@84C.

@07V 7=0G=>W 0@B5@V0;L=>W 3V?>B5=7VW 01> 0B@V>25=B@8:C;O@=>W 1;>:048 28A>:>3> ABC?5=O =5>1EV4=> 70AB>A>2C20B8 70A>18, I> ?V428ICNBL 0@B5@V0;L=89 B8A:

(AC48=>72C6C20;L=V), 01> :0@4V>AB8@8 2V4?>2V4=>. @8 0A8AB>;VW >4=>G0A=> 7

70AB>AC20==O< 728G09=8E 70E>4V2 A;V4 70AB>AC20B8 β-04@5=5@3VG=C AB8,

V7?>@>B5@5=>;C 3V4@>E;>@84), V=HV 70A>18, A?@O<>20=V =0 ?V428I5==O 0@B5@V0;L=>3> B8A:C 01> ?@>25AB8 2V4=>2;5==O A5@F52>W 4VO;L=>ABV B0 48E0==O.

5@0?0E;>@84 =5 282>48BLAO 70 4>?><>3>N 35<>4V0;V7C.

>1VG=V @50:FVW.

!5@F52>-AC48==0 A8AB5<0: AB5=>:0@4VO, 0@B5@V0;L=0 3V?>B5=7VO, A8=>0B@V0;L=0 B0 AV- 1;>:040 , II 01> III ABC?5=O, 1@048:0@4VO, 1@0480@8B2>3> 2C7;0, 0A8AB>;VO; @878:

703>AB@5==O/@>728B:C A5@F52>W =54>AB0B=>ABV, >@B>AB0B8G=V @50:FVW; B0EV:0@4VO, 1V;L 70 3@C4=8=>N, V=D0@:B:0@40, 2V4GCBBO A5@F518BBO, ?5@8D5@8G=V =01@O:8 I8:>;>B>;, A8=>?5, ?@8?;828.

"@02=89 B@0:B: 48A:>@B C 682>BV/1V;L, H;C=:>2>-:8H:>2V @>7;048, B0:V O: =C4>B0, 1;N20==O, <5B5>@87<; 0B=>VO :8H5G=8:C, :8H:>20 =5?@>EV4=VABL, 70?>@; ACEVABL C @>BV, 3V?5@?;07VO

OA5= (3V=3V2VB V :@>2>B5G0).

5@2>20 A8AB5<0: ?>@CH5==O <>7:>2>3> :@>2>>1V3C, A?;CB0=VABL A2V4<>ABV, ?>@CH5==O @V2=>2038, AB<;N20=VABL, 157A>==O, =5@2>7=VABL,<07>2V AC4<8, ?A8E>78, =59@>?0BVO,

5:AB@0?V@0<, A=>;82VABL, 3>;>2=89 1V;L, 70?0<>@>G5==O, ?0@5AB57VW, B@5<>@.

@30=8 A;CEC B0 25AB81C;O@=89 0?0@0B: 472V= C 2CE0E, 25@B83>.

8E0;L=0 A8AB5<0, >@30=8 3@C4=>W ;;VB:8 B0 A5@54>ABV==O: 1@>=E>A?07<, 48A?=>5.

8@:8 B0 A5G>284V;L=0 A8AB5<0: =8@:>20 =54>AB0B=VABL.

!5G>AB0B520 A8AB5<0: 5@5:B8;L=0 48ADC=:FVO, 2 B>28?CA:0==O, ?>@CH5==O <5=AB@C0;L=>3> F8;;C; C ?0FVT=BV2 ;VB=L>3> 2V:C ?@8 4>23>B@820;V9 B5@0?VW @>72820;0AO 3V=5:×0ABVO,

O:0 ?>2=VABN<8=0;0 ?VA;O 2V4@5O.

?>@=>-@CE>20 A8AB5<0: <07>20 A;01:VABL,

(:V@0 B0 ?V4H:V@=0 ;;VB:>28=0: 28A8?0==O =0 H:V@V (2 B>2V4GCBBO A25@156C, A25@1V6, 0;>?5FVO, 3V?5@3V4@>7, ?>@CH5==O ?V3<5=B0FVW, 5@8B@<5;0;3VO, @<=0 5@8B5<0, A8=4@<×

!BV25=A0-6>=A>=0, =01@O: 2V=:5, D>B>45@<0B8B8, A8=FV, ?C@?C@0.

>@CH5==O >128=, <5B01>;V7 3V?5@:0;VT

5?0B>1V;V0@=0 A8AB5<0: ?V428I5==O @V2=O B@0=A0W D>AD0B078 B0 1V;V@C1V=C; <>6;82V CH:>465==O ?5GV=:8 7 ;;V=VG=8<8 ?@>O20<8 (?>30=5 A0<>?>GCBBO, ?V428I5==O B5 1V;L C ?@02>

450:8E 28?04:0E FV 7 A0<>ABV9=> 7=8:0NBL ?@8 ?@>4>265==V B5@0?VW.

3V?5@GCB;82VABL, 0;5@3VG=89 35?0B8B.

=HV: =5GVB:VABL 7>@C, ?V428I5==O @V2=O ?@>;0:B8=C 2 ?;072V, 7=865==O B>;5@0=B=>ABV 4> 3;N:>78.

>2V4><;O;>AO ?@> ?0@0;VG (B5B@0?0@57), 0A>FV9>20=89 7 :><1V=>20=8< 70AB>AC20==O<

25@0?0;EVF8=C. &5 <>65 1CB8 7C<>2;5=> ?@>=8=:5==O< :>;EVF8=C G5@57 35<0B>5=F5D0;VG=89 10@T@ 2=0A;V4>: ?@83=VG5==O 25@0?0< CYP3A4 B0 P-qp, B><1V=>20=5 70AB>AC20==O

:>;EVF8=C B0 25@0?0<5=4>20=5.

"5@ABV.5 @>:V2.

#<>28 715@V30==O. >@83V=0;L=V9 C?0:>2FV ?@8 B525 >!.
15@V30B8 2 =54>ABC?=>

#?0:>2:0. > 10 B01;5B>: C 1;VAB5@V, ?> 5 1;VAB5@V2 C ?0GFV.

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

8@>1=8:. C1;VG=5 0:FV>=5@=5 B>20@8AB2> «0C:>2>-28@>1=8G89 F5=B@ «>@I03V2AL:89 EV-D0@
<0F52B8G=89 702>4».

VAF57=0E>465==O28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

#: @0W=0, 03134, <. 8W2, 2C;. 8@C, 17.

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

%
(VERAPAMIL HYDROCHLORIDE)

!>AB02:

459AB2CNI55 25I5AB2>: 25@0?0<8;0 384@>E;>@84;

1 B01;5B:0 A>45@68B 80 <3 25@0?0<8;0 384@>E;>@840 2 ?5@5AG5B5 =0 100 % ACE>5 25I5AB2>;

2A?><>30B5;L=K5 25I5AB20: :@0E<0; :C:C@C7=K9, ;0:B>7K <=>384@0B, :>?>284>=, <03=8O

AB50@0B.

;5=>>1@07CNI55 ?>:@KB85: 384@>:A8?@>?8;<5B8;F5;;N;>70, ;0:B>7K <=>384@0B, B8B0=0 48>:A84
(171), ?>;8MB8;5=3;8>;L, B@80F5B8=.

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

A=>2=K5 D878:>-E8<8G5A:85 A2>9AB20: :@C3;K5 B01;5B:8, ?>:@KBK5 ?;5=>G=>9 >1>;>G:>9, 15;>3>

F25B0, A 42>O:>2K?C;>9 ?>25@E=>ABLN. 0 ?>?5@5G=>< A@575 284=K 420 H0@0 @07=>9

AB@C:BC@K.

\$0@<0:>B5@0?52B8G5A:0O 3@C??0. !5;5:B82=K5 0=B03>=8ABK :0;LF8O A ?@58>4 ""% C08D A01.

\$0@<0:>;>38G5A:85 A2>9AB20.

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

5@0?0<8;0 384@>E;>@84 O2;O5BAO A5;5:B82=K< 1;>;0B>@<< :0;LF852KE :0=0;>2 L B8?0 I :;0AA0,

>.07K205B 0=B80=38=0;L=>5 8 38?>B5=782=>5 459AB28O. ;>:8@C5B ?>B5=F80;7028A8ABC?;5=85

8>=>2 :0;LF8O 2=CB@L :;5B>;, 2 G0AB=>AB8, :0@48><8>F8B>2 8 :;5B>: 3;04:8E AC4>2,

:>=F5=B@0F8O :0;LF8O 2 :@>28 ?@8 MB<< =5 <5=O5BAO.

=B80=38=0;L=>5 459AB285 ?@5?0@0B0 @50;87C5BAO 1;03>40@O A=865=8N B>=CA0 :>@>=0@=KE 8

?5@8D5@8G5A:8E 0@B5@80;L=KE A>AC4>2, C;CGH5=8N :@>2>A=0165=8O A5@45G=>9< G8A;5 2

8H5<878@>20==KE CG0AB:0E; A=8605B ?>B@51=>ABL <8>:0@40 2 :8A;>@>45, C<5=LH0O A>:@0B8

<>ABL <8>:0@40 8 C25;8G820O :>@>=0@=K9 :@>2>B>.: =B80=38=0;L=K9 MDD5:B >1CA;>2;5= B0:65

207>48;0B8@CNI8< ?5@8D5@8G5A:8< 459AB285<, GB> ?@82>48B : C<5=LH5=8N ?>AB=03@C7:8 8

?>B@51=>AB8 <8>:0@40 2 :8A;>@>45.

5@0?0<8;0 384@>E;>@84 >B=>A8BAO : 0=B80@8B<8G5A:8< ?@5?0@0B0< IV :;0AA0. =B80@8B

<8G5A:89 MDD5:B >1CA;>2;5= 1;>;:04>9 :0;LF852KE :0=0;>2 2 :;5B:0E ?@>2>4OI59 A8AB50B@80;L=><

8 0B@8>25=B@8:C;O@=>< C7;0E), GB> ?@82>48B : 70<54;5=8N 02B><0B87<0 -;>;5B>: A8=CA>2>3>

C7;0, M:B>?8G5A:8E >G03>2 2 ?@54A5@48OE 8 A:>@>AB8 ?@>2545=8O 2>71C645=8O G5@57

0B@8>25=B@8:C;O@=K9 C75;. A;54AB285 MB>3> C25;8G8205BAO MDD5:B82=K9 @5D@0:B5@=K9

?5@8>4 2 A8=CA>2<< 8 0B@8>25=B@8:C;O@=>< C7;0E, 70<54;O5BAO A8=CA>2K9 @8B<, C

<5=LH05BAO G0AB>B0 A5@45G=KE A>:@0I5=89.
=B838?5@B5=782=>5 459AB285 25@0?0<8;0 384@>E;>@840 >1CA;>2;5=> @0AA;01;5=85< 3;04:8E
AC4>2, A=865=85< >1I53> ?5@8D5@8G5A:>3> A>AC48AB>3> A>?@>B82;5=8O, 0@B5@80;L=>3>
402;5=8O, :0: ?@028;>, 157 @0728B8O ?>ABC@0;L=>9 38?>B5=788 8 @5D;5:B>@=>9 B0E8:0@488;
1@048:0@48O (G0AB>B0 A5@45G=KE A>:@0I5=89 <5=55 50 2 <8=CBC) @0728205BAO @54:>.

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

>A;5 ?5@>@0;L=>3> ?@85<0 2 B>=:< :8H5G=8:5 2A0AK205BAO 1>;55 90 % 22545==>9 4>7K 25@0?0
<8;0 384@>E;>@840. @5?0@0B <5B01>;878@C5BAO ?@58 2 ?5G5=8 2A;54AB285 8=B5=A82=>3>
<5B01>;87<0 ?@8 ?5@2>< ?@>E>645=88 G5@57 2>@>B=CN A8AB54>ABC?=>ABL ?@5?0@0B0
A>AB02;O5B 20-35 %. 0:A8<0;L=0O :=F5=B@0F8O 25@0?0<8;0 384@>E;>@840 2 ?;07<5 :@>28 >B
<5G05BAO G5@57 1-2 G0A0 ?>A;5 ?@85<0 ?@5?0@0B0.
!B5?5=L A=865=8O 402;5=8O :@>28 =5 7028A8B >B :=F5=B@0F88 5@0?0<8;0 384@>E;>@840 2 ?;07<5
:@>28.

! 15;:0<8 :@>28 A2O7K205BAO ?@81;878B5;L=> 90 % ?@5?0@0B0.

5@0?0<8;0 384@>E;>@84 ?@=>8:05B G5@57 ?;0F5=BC 8 M:A:@5B8@C5BAO 2 3@C4=>5 <>;>:
!@54=89 ?5@8>4 ?>;C2K2545=8O A>AB02;O5B 2,8-7,4 G0A0 ?>A;5 ?5@2>3> ?@85<0 8 4,5-12 G0A>2 =0
D>=5 4;8B5;L=>3> ?@85<0. # ?0F85=B>2 AB0@H59 2>7@0AB=>9 3@C?K ?5@8>4 ?>;C2K2545=8O
<>65B C25;8G820BLAO.

5402=> ?>;CG5==K5 40==K5 A2845B5;LAB2CNB, GB> =5B @07=8FK 2 D0@<0:>:8=5B8:5 25@0?0<8;0 C
;N459 A> 74>@>2K<8 ?>G:0<8 8 C ?0F85=B>2 A B5@<8=0;L=>9 AB04859 ?>G5G=>9
=54>AB0B>G=>AB8.

?0F85=B>2 A ?5G5=>G=>9 =54>AB0B>G=>ABLN ?5@8>4 ?>;C2K2545=8O C25;8G8205BAO 4> 14-16
G0A>2, >1J5< @0A?@545;5=8O C25;8G8205BAO, ?;07<5==K9 ;;8@5=A A>AB02;O5B ?@8<5@=> 30 %
=>@MB>7C 4;O B0:8E ?0F85=B>2 C<5=LH0NB 4> 1/3 >1KG=>9 ACB>G=>9 4>7K.

@5?0@0B 2K2>48BAO ?@58 ?>G:0<8 (70 %), G0AB8G=> :8H5G=8:>

;8=8G5A:85 E0@0:B5@8AB8:8.

>:070=8O.

- @B5@80;L=0O 38?5@B5=78O.
- □H5<8G5A:0O 1>;57=L A5@4F0, 2;:NG0O AB018;L=CN AB5=>:0@48N =0?@O65=8O,
=5AB018;L=CN AB5=>:0@48N (?@>3@5AA8@CNI0O AB5=>:0@48O, AB5=>:0@48O ?>:>O),
207>A?0AB8G5A:CN AB5=>:0@48N (20@80=B=0O AB5=>:0@48O, AB5=>:0@48O @8=F<5B0;0),
?>AB8=D0@:B=CN AB5=>:0@48N C ?0F85=B>2 157 A5@45G=>9 =54>AB0B>G=>AB8, 5A;8 =5
?>:070=K □-04@5=>1;:>:0B>@K.
- □@8B<88: ?0@>:A87<0;L=0O =0465;C4>G:>20O B0E8:0@48O, <5@F0=85/B@5?5B0=85
?@54A5@489 A 1KAB@>9 0B@8>25=B@8:C;O@=>9 ?@>2>48<>ABLN (70 8A;:NG5=85< A8=4@<>0
>;LD0-0@:8=A>=0-#09B0 WPW).

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

- 8?5@GC2AB28B5;L=>ABL : 25@0?0<8;C 8;8 : 4@C38< :=5=B0< ?@5?0@0B0.
- 0@48>35==K9 H>:.
- AB@0O D070 8=D0@:B0 <8>:0@40 A >A;>6=5=8O<8 (1@048:0@48O < 50 C4/<8=, 0@B5@80;L=0O
38?>B5=78O (A8AB>;8G5A:>5 402;5=85 =865 90 << @B.AB.), =54>AB0B>G=>ABL ;52>3>
65;C4>G:0).
- "O65;K5 =0@CH5=8O ?@>2>48<>AB8: A8=>0B@80;L=0O 8 0B@8>25=B@8:C;O@=0O (AV)
1;:>:040
-AB5?5=8 (70 8A;:NG5=85< ?0F85=B>2 A 8A:CAAB25==K< 2>48B5;5< @8B<0).
- !8=4@<< A;01>AB8 A8=CA>2>3> C7;0 (70 8A;:NG5=85< ?0F85=B>2 A 8A:CAAB25==K< 2>48B5;5<
@8B<0).
- !5@45G=0O =54>AB0B>G=>ABL A> A=865=85< D@0:F88 2K1@>A0 <5=55 35 % 8/8;8 402;5=85< 2
;53>G=>9 0@B5@88 2KH5 20 << @B. AB. (5A;8 B>;L:> 2B>@8G=0O =0465;C4>G:>20O B0E8:0@48O
=5 ?>4405BAO 2;8O=8N B5@0?88 25@0?0<8;<<).

- 5@F0=85/B@5?5B0=85 ?@54A5@489 ?@8 =0;8G88 4>?>;=8B5;L=KE ?@>2>4OI8E ?CB59 (=0 D>=5 A8=4@>>2 WPW 8 LGL). # B0:8E ?0F85=B>2 ?@8 ?@8<5=5=88 25@0?0<8;0 384@>E;>@840 5ABL @8A: @0728B8O 65;C4>G:>2>9 B0E80@8B<88, 2::;NG0O 65;C4>G:>2CN D81@8;;OF8N.
- 4=>2@5<5==>5 8A?>;L7>20=85 1;>;0B>@>2 □-04@5=>@5F5?B>@>2 4;O 2=CB@825==>3> 22545=8O (70 8A:;NG5=85< 8=B5=A82=>9 B5@0?88).

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

! □-04@5=>1;>;:0B>@0<8: C25;8G8205B 2708<=>5 ?>402;ONI55 459AB285 =0 02B><0B87< A8=>0B@80;L=>3> C7;0, V-?@>2>48<>ABL 8 A>:@0B8<>ABL <8>:0@40, 2A;54AB285 MB>3> ?>2KH05BAO @8A: @0728B8O 2K@065==>9 0@B5@80;L=>9 38?>B5=788, V- 8S-1;>;:04, 1@048:0@488, A5@45G=>9 =54>AB0B>G=>AB8, >A>15==> ?@8 ?@8<5=5=88 2KA>:8E 4>7 □-04@5=>1;>;:0B>@>2 8;8 ?@8 8E 2=CB@825==>< 22545=88.

A>1CN 3@C??C @8A:0 A>AB02;ONB ?0F85=BK A ?@87=0:0<8 E@>=8G5A:>9 A5@45G=>9 =54>AB0B>G=>AB8, 2K@065==>9 :0@48><8?>0B88 8;8 B5, :>B>@K5 =5402=> ?5@5=5A;8 8=D0@:B <8>:0@40. ><18=8@>20==CN B5@0?8N 5@0?0<8;0 384@>E;>@840 A □-04@5=>1;>;:0B>@0<8 A;54C5B ?@>2>48BL B>;L:> ?> G5B:8< ?>:070=8O< 8 ?>4 AB@>38< :>=B@>;5< 2@0G0.

! 0=B838?5@B5=782=K<8 ?@5?0@0B0<8 (=0?@8<5@, 207>48;0B0B>@K, 8=3818B>@K \$, 48C@5B8:8, α-1;>;:0B>@K, ?@07>78= 8 B5@07>78=): 25@0?0<8;0 384@>E;>@84 ?>B5=F8@C5B 8E 459AB285.

! B@8F8.;8G5A:8<8 0=B845?@5AA0=B0<8, =59@>;5?B8:0<8: ?>B5=F8@>20=85 38?>B5=782=>3> 459AB28O 25@0?0<8;0 384@>E;>@840.

! A5@45G=K<8 3;8:>7840<8 (=0?@8<5@, 483>:A8=><): A;54C5B CG8BK20BL, GB> 2 =0G0;5 ;5G5=8O

(1-O =545;O) C@>25=L 483>:A8=0 2 AK2>@>B:5 :@>28 ?>2KH05BAO =0 50-70 %, ?>MB> >B:>@@5:B8@>20BL 4>7C 483>:A8=0, 0 53> C@>25=L 2 AK2>@>B:5 :@>28 ?5@8>48G5A:8 :>=B@>;8@>20BL, >A>15==> 2 =0G0;5 ;5G5=8O.

! 0=B80@8B<8G5A:8<8 ?@5?0@0B0<8 I-III ;;0AA0 (2 B>< G8A;5 0<8>40@>=><): =5 @5:><5=4C5BAO >4=>2@5<5==>5 ?@8<5=5=85.

! 487>?8@0<84>< (@8B<8;5=><): =5 A;54C5B ?@8<5=OBL >4=>2@5<5==>, ?@85< 487>?8@0<840 =04> ?@5:@0B8BL 70 48 G0A>2 4> =0G0;0 ?@8<5=5=8O 25@0?0<8;0 384@>E;>@840, 8 2>7<>6=> 2>7>1=>28BL =5 @0=55 G5< G5@57 24 G0A0 ?>A;5 ?@5:@0I5=8O ?@85<0 25@0?0<8;0 384@>E;>@840.

! D;5:08=84> ACI5AB25==> 87<5=O5BAO 2708<=>5 ?>402;ONI55 459AB285 =0 <8>:0@4, 70<54;O5BAO 0B@8>25=B@8:C;O@=0O ?@>2>48<>ABL 8 C25;8G8205BAO ?@>4>;68B5;L=>ABL @5?>;O@870F88.

! E8=848=> C<5=LH5=85 ;;8@5=A0 E8=848=0 (~ 35 %) ?@8 ?5@>@0;L=>< ?@85<5. >7<>6=> @0728B85 0@B5@80;L=>9 38?>B5=788, 0 C ?0F85=B>2 A 38?5@B@>D8G5A:>9 >1AB@C:B82=>9 :0@48> <8>?0B859 >B5: ;53:8E. >MB>10 ?@5?0@0B0 2<5AB5.

! ?5@>@0;L=K<8 ?@>B82>70G0B>G=K<8 ?@5?0@0B0<8, 3840=B>8=><, A0;8F8;0B0<8, AC;LD0=8;0 <840<8 8 ?@>872>4=K<8 AC;LD>=8;<>G528=K: 2A;54AB285 2KA>:>9 AB5?5=8 A2O7K20=8O 25@0?0 <8;0 A 15::0<8 ?;0728 53> A;54C5B A >AB>@>6=>ABLN =07=0G0BL ?0F85=B0<, :>B>@K5 ?@8=8<0NB 4@C385 ?@5?0@0BK, 8<5NI85 40==K5 A2>9AB20.

! A>;O<8 :0;LF8O 8 28B0<8=>< D: D0@<0>;>38G5A:89 MDD5:B 25@0?0<8;0 384@>E;>@840, 25@>OB=>, C<5=LH05BAO.

! ?@>?@0=>;>;><, <5B>?@>;>;> 25@0?0<8;0 384@>E;>@84 <>65B A=860BL 8E ;;8@5=A.

! @8D0<, D5=>10@18B0;> <>3CB A=860BL MDD5:B82=>ABL ?@5?0@0B0 :0: 8=4C:B>@K<8:@>A> <0;L=8E D5@<5=B>2.

! A>;O<8 ;8B8O, B5>D8;;8=> ?>4 459AB285< 25@0?0<8;0 :>=F5=B@0F8O 2 AK2>@>B:5 :@>28 <>65B 87<5=OBLAO, ?>MB>

! F8:;>A?>@8=><, M25@>;8<, A8@>;8<, B0:@>;8<, 8=3818B>@0<8 A5@>B>=8=>2KE @5F5?B>@>2 (B0:8< :0: 0;<>B@8?B0=), :0@10<075?8=>< 8 B5>D8;;8=>25@0?0<8; ?@82>48B : ?>2KH5=8N 8E C@>2=O 2 AK2>@>B:5 :@>28 ?@8 >4=>2@5<5==>< ?@8<5=5=88.

! :>;E8F8=>25@0?0<8; <>65B ?@825AB8 : CA8;5=8N 53> 459AB28O. ><18=8@>20==>5 ?@8<5=5=85 MB8E ?@5?0@0B>2 =5 @5:><5=4C5BAO.

! 0=B03>=8AB0<8 H2-@5F5?B>@>2, F8<5B848=> 2>7<>6=> ?>2KH5=85 :>=F5=B@0F88 25@0?0<8;0 2 ?;07<5 :@>28.

! 0=B8@5B@>28@CA=K<8 ?@5?0@0B0<8 (B0:8<8 :0: @8B>=028@, 8=48=028@): 2>7<6=>
?>2KH5=85 :>=F5=B@0F88 25@0?0<8;0 2 ?;07<5 :@>28. >MB>;L7>20BL 5@0?0<8;0 384@>E;>@84 2
MB>9 :><18=0F88 A;54C5B A >AB>@>6=>ABLN 8;8 53> 4>70 4>;6=0 1KBL A=865=0.
! 8=3818B>@0<8 ->@54C:B07K (A8<20AB0B8=, 0B>@20AB0B8=, ;>20AB0B8=): ;5G5=85 AB0B8=0<8
A;54C5B =0G8=0BL A A0=87:8E 2>7<6=>6=KE 4>7 8 ?>AB5?5=> 8E C25;8G820BL. A;8 ?0F85=BC,
:>B>@K9 C65 ?@8=8<05B 25@0?0<8; , =5>1E>48<> =07=0G5=85 AB0B8=>2, A;54C5B CG5ABL
=5>1E>48<>5 A=865=85 8E 4>7K 8 ?>4>1@0BL 4>78@>2:C 2 A>>B25BAB288 A :>=F5=B@0F859
E>;5AB5@8=0 2 ?;07<5 :@>28.
! A8<20AB0B8=>< (2 1>;LH8E 4>70E): ?>2KH05BAO @8A: <8>?0B88, @014><8>;870. >78@>2:0 A8
<20AB0B8=0 4>;6=0 1KBL A>>B25BAB25=> >B:>@>5:B8@>20=0.
! D;C20AB0B8=><, ?@020AB0B8=>< 8 @>7C20AB0B8=>>=8 =5 <5B01>;878@CNBAO A8AB5<>9
CYP3A4 8 2 A2O78 A MB8< ?@0:B8G5A:8 =5 2708<>459AB2CNB A 25@0?0<8;>
! ACIAB@0B0<8 F8B>E@><0 450 87>M=78<0 34, =0?@8<5@ 8=3818B>@0<8 !SE (2 B.G. ;>20AB0B8=,
A8<20AB0B8=, 0B>@20AB0B8=): 2>7<6=> ?>2KH5=85 C@>2=O MB8E ;5:0@AB25==KE A@54AB2 2
?;07<5 :@>28, GB> ?>2KH05B @8A: B>:A8G5A:>3> ?>@065=8O
! 8=30;OF8>==K<8 0=5AB5B8:0<8 8;8 A 1;:>:0B>@0<8 =59@>9 ?5@540G8: 4>7K ?@5?0@0B>2
A;54C5B >B:>@>5:B8@>20BL, GB>1K 871560BL ?>402;ONI53> 459AB28O =0 A5@45G=CN
45OB5;L=>ABL.
! <8>@5:0:A0=B0<8: ?>B5=F8@C5B 8E 459AB285.
! <0:@>;840<8 (=0?@8<5@, M@8B@><8F8= 8;8 :;0@8B@><8F8=): 87-70 2708<=>3> 2;8O=8O
?>2KH05BAO C@>25=L 25@0?0<8;0 2 ?;07<5 :@>28.
! 0=B848015B8G5A:8<8 ?@5?0@0B0<8 (3;81C@84): ?>2KH05BAO !<0E 3;81C@840 =0 28 %.
! 4>:A>@C18F8=>< (?5@>@0;L=>): ?>2KH05BAO 18>4>ABC?=>ABL 8 <0:A8<0;L=K9 C@>25=L
4>:A>@C18F8=0 2 ?;07<5 :@>28 C ?0F85=B>2 A <5;:>;5B>G=K< @0:>< ;53:8E.
! ?@5?0@0B0<8 725@>1>O ?@>4K@O2;5==>3>: C<5=LH05BAO ?;>I04L ?>4 :@82>9 :>=F5=B@0F8O-
2@5<0E.
! @5=B35=>:>=B@0AB=K<8 A@54AB20<8: 2>7<6=> ?>B5=F8@>20=85 ?>402;ONI53> 2;8O=8O
25@0?0<8;0 =0 02B><0B87< A8=>0B@80;L=>3> C7;0, V-?@>2>48<>ABL 8 A>:@0B8<>ABL <8>:0@40.
! MB0=>;> 25@0?0<8; 7045@68205B @0A?04 8 ?>2KH05B 53> C@>25=L 2 ?;07<5 :@>28, B5< A00.
! 3@59?D@CB>2K< A>:> ?>2KH05BAO 18>4>ABC?=>ABL 25@0?0<8;0 =0 30 %.
! AC;LD8=?8@07>=>?>2KH5=85 ;8@5=A0 ?5@>@0;L=>3> 25@0?0<8;0 2 3 @070, 18>4>ABC?=>AB8
=0 60 %. >7<6=> A=865=85 38?>B5=782=>3> MDD5:B0.
! 0F5B8;A0;8F8;>2>9 :8A;>B>9: ?>2KH5=85 @8A:0 :@>2>B5G5=89.
! 4838B>:A8=>C<5=LH5=85 ;8@5=A0 4838B>:A8=0 (~ 27 %) 8 M:AB@0@5=0;L=>3> ;8@5=A0 (~ 29 %).
! IC=A?8@=>=>C25;8G5=85 AUC 8 !<0E 2 3-4 @070.
! 8<8?@0<8=> C25;8G5=85 AUC (~ 15 %) 8<8?@0<8=0 157 2;8O=8O =0 0:B82=K9 <5B01>;8B 4578?@0
<8=.
! <8407>;0<>C25;8G5=85 AUC 2 3 @070 8 !<0E 2 2 @070.
AA;54>20=8O <5B01>;87<0 25@0?0<8;0 384@>E;>@840 in vitro ?>:070;8, GB> >=<5B01>;878@C5BAO
F8B>E@><< 450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 8 CYP2!18. 5@0?0<8; O2;O5BAO 8=3818B>@><
D5@<5=B>2 CYP3A4 8 -3;8:>?@>B58=>2 (-gp). !>>1I0;>AL > ;8=8G5A:8 206=K5 2708<>459AB28O A
8=3818B>@0<8 CYP3A4, A>?@>2>6402H85AO ?>2KH5=85< C@>2=O 25@0?0<8;0 2 ?;07<5 :@>28,
B>340 :0: 8=4C:B>@K CYP3A4 2K7K20;8 A=865=85 ?;07<5==KE C@>2=59 25@0?0<8;0 384@>E;>@840,
?>MB>1E>48<> ?@>2>48BL <=>8B>@8=3 2708<>459AB28O A 4@C38<8 ;5:0@AB25==K<8 A@54AB20
<8.

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

@5?0@0B A;54C5B ?@8<5=OBL A >AB>@>6=>ABLN ?0F85=B0< A >AB@K< 8=D0@:B>< <8>:0@40,
>A;>6=5==K< 1@048:0@4859, 2K@065==>9 0@B5@80;L=>9 38?>B5=7859 8;8 48ADC=:F859 ;52>3>
65;C4>G:0.
5@0?0<8;0 384@>E;>@84 2;8O5B =0 0B@8>25=B@8:C;O@=K9 8 A8=>0B@80;L=K9 C7;K 8
?@>;>=38@C5B 2@525=B@8:C;O@=>9 ?@>2>48<>AB8. @8<5=OBL A >AB>@>6=>ABLN ?0F85=B0< A
V-1;>:04>9 I AB5?5=8, 87-70 2>7<6=>3> @0728B8O 0B@8>25=B@8:C;O@=>9 1;>:04K II 8;8
III AB5?5=8 8;8 >4=>?CG:>2>9, 42>?CG:>2>8 8;8 B@8?CG:>2>8 1;>:04K =>6:8 8A0, GB> B@51C5B >B
<5=K ?>A;54CNI8E 4>7 25@0?0<8;0 384@>E;>@840 8 =07=0G5=8O A>>B25BAB2CNI59 B5@0?88 2

A;CG05 =5>1E>48<>AB8.
5@0?0<8;0 384@>E;>@84 2;8O5B =0 0B@>25=B@8:C;O@=K9 8 A8=>0B@80;L=K9 C7;K 8 8=>340
<>65B A?@>2>F8@>20BL 2>7=8:=>25=85 0B@>25=B@8:C;O@=>9 1;>:04K II 8;8 III AB5?5=8,
1@048:0@488, 0A8AB>;88. >;55 25@>OB=>, GB> B0:85 A82 A A8=4@><< A;01>AB8 A8=CA>2>3> C7;0
(A8=>0B@80;L=0O C7;>20O 1>;57=L), :>B>@K9 G015 2AB@5G05BAO C ?0F85=B>2 ?>68;>3>
2>7@0AB0.

A8AB>;8O C ?0F85=B>2, =5 8<5NI8E A8=4@><0 A;01>AB8 A8=CA>2>3> C7;0, >1KG=> :@0B:>2@5
<5==0O (=5A:>;L:> A5:C=4 8;8<5=LH5), A> A?>=B0==K< 2>72@0I5=85< : 0B@>25=B@8:C;O@=> 8;8
=>@<0;L=> A8=CA>2> @8B<C. A;8 MB> O2;5=85 =5 <8<>;5B=>5, A;54C5B =5<54;5==> =0G0BL
A>>B25BAB2CNICN B5@0?8N (A1>G=K5 @50:F88»).

=B80@8B<8G5A:85 A@54AB20, □-04@5=>1;>:0B>@K. 708<=>5 CA8;5=85 :0@48>20A:C;O@=>3>
459AB28O (?>2KH5=85 AB5?5=8 0B@>25=B@8:C;O@=>9 1;>:04K 2KA>:>9 AB5?5=8, 7=0G8B5;L=>5
A=865=85 G0AB>BK A5@45G=KE A>:@0I5=89, ?>O2;5=85 A5@45G=>9 =54>AB0B>G=>AB8,
7=0G8B5;L=>5 A=865=85 0@B5@80;L=>3> 402;5=8O). !8<0B8G5A:0O 1@048:0@48O (36 C4/<8=) A
1;C640NI8< 2>48B5;5< @8B<0 ?@54A5@489 =01;N40;0AL C ?0F85=B>2, :>B>@K5 ?>;CG0;8
A>?CBAB2CNICN B5@0?8N 3;07=K<8 :0?;O<8 A B8<>;>;< (□-04@5=>1;>:0B>@) =0 D>=5 ;5G5=8O
25@0?0<8;0 384@>E;>@84>

@8 >4=>2@5<5==<< ?@8<5=5=88 25@0?0<8;0 A 483>:A8=< A;54C5B C<5=LH8BL 4>7C 483>:A8=0 (A
5@54 =0G0;>< ;5G5=8O 25@0?0<8;>< =5>1E>48<> :>20BL A5@45G=CN =54>AB0B>G=>ABL C
?0F85=B>2 A D@0:F859 2K1@>A0 1>;55 35 % 8 045:20B=> :>=B@>;8@>20BL 8E A>AB>O=85 2
B5G5=85 2A53> ?5@8>40 ;5G5=8O.

5@0?0<8;0 384@>E;>@84 A;54C5B ?@8<5=OBL A >AB>@>6=>ABLN ?@8 =0;8G88 701>;520=89 A
=0@CH5=8O<8 =5@2=>-9 ?@>2>48<>AB8 ?0F85=B0< A: Myastenia gravis, A8=4@><< 0<15@B0-B>=0,
?@>3@5AA8@CNI59 9 48AB@>D859 NH5=0).

!>AB>@>6=>ABLN A;54C5B =07=0G0BL 5@0?0<8;0 384@>E;>@84 ?0F85=B0< A =0@CH5=85<
DC=:F88 ?5G5=8 (@5:><5=4C5BAO A=878BL 4>7C 4> 30 % >B >1KG=>9 ACB>G=>9); A ?>G5G=>9
=54>AB0B>G=>ABLN (BI0B5;L=> :>=B@>;8@>20BL ?@>4>;68B5;L=>ABL Q-T, 0 B0:65 4@C385
?@87=0:8 2>7<>6=>9 ?5@54>78@>2:8 25@0?0<8;0 384@>E;>@840).

!;54C5B :>=B@>;8@>20BL ?@>4>;68B5;L=>ABL Q-8=B5@20;0 =0 -, 0 B0:65 4@C385 ?@87=0:8 2>7
<>6=>9 ?5@54>78@>2:8 5@0?0<8;0 384@>E;>@840 C ?0F85=B>2 (@53C;O@=K9 :>=B@>;L , !!).
@8 =07=0G5=88 5@0?0<8;0 384@>E;>@840 A;54C5B CG8BK20BL, GB> ;8F0 ?>68;>3> 2>7@0AB0
<>3CB 8<5BL ?>2KH5==CN GC2AB28B5;L=>ABL : 459AB28N ?@5?0@0B0, 4065 ?@8 CA;>288
>1KG=>3> 4>78@>20=8O.

@5?0@0B A>45@68B ;0:B>7C, ?>MB> =5 A;54C5B ?@8<5=OBL ?0F85=B0< A @54:8<8 =0A;54AB25==K
<8 D>@<0<8 =5?5@5=>A8<>AB8 30;0:B>7K, =54>AB0B>G=>ABLN ;0:B07K 8;8 A8=4@><< 3;N:>7>-
30;0:B>7=>9 <0;L01A>@1F88.

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

'5B:85 8 E>@>H> 87CG5==K5 40==K5 ?@8<5=5=8O ?@5?0@0B0 15@5<5==K< 65=I8=0<
>BACBAB2CNB. >MB>

5@0?0<8; 8 53> <5B01>;8BK ?@>=8:0NB 2 3@C4=>5 <>;>.: >70 25@0?0<8;0, :>B>@0O ?>?0405B 2
>@30=87< =>2>@>645==>3>, =87:0O (0,1-1 % 4>7K, ?@8=OB>9 <0B5@LN), ?>MB>

#G8BK20O @8A: ?>O2;5=8O A5@L57=KE ?>1>G=KE @50:F89 C =>2>@>645==KE, =0E>4OI8EAO =0
3@C4=>< 2A:0@<;820=88, 25@0?0<8; 2 ?5@8>4 :>@<;5=8O 3@C4LN <>6=> ?@8<5=OBL B>;L:> 2
A;CG05 :@09=59 =5>1E>48<>AB8 4;O <0B5@8.

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

7-70 0=B838?5@B5=782=>3> MDD5:B0 25@0?0<8;0 384@>E;>@840, 2 7028A8<>AB8 >B
8=48284C0;L=>9 @50:F88, A?>A>1=>ABL C?@02;OBL B@0=A?>@B=K<8 A@54AB20<8, 4@C38<8
<5E0=87<0<8 8;8 @01>B0BL 2 ?>0A=KE CA;>28OE <>65B 1KBL =0@CH5=0. A>15==> MB> :0A05BAO
=0G0;L=>9 D07K ;5G5=8O, ?@8 ?>2KH5=88 4>7K, ?@8 87<5=5=88 38?>B5=782=>3> ?@5?0@0B0, 0
B0:65 ?@8 >4=>2@5<5==<< ?@8<5=5=88 ?@5?0@0B0 A 0;>3>;53>;O <>65B CA8;820BLAO.

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

>7K ?>418@0BL 8=48284C0;L=> 4;O :064>3> ?0F85=B0.
"01;5B:8 3;>B0BL F5;8:<, =5 @0AA0AK20BL, =5 @07652K20BL, =5 87<5;LG0BL, =5 45;8BL =0 G0AB8;
70?820BL 4>AB0B>G=K< :>;8G5AB2>< 684:>AB8 (=0?@8<5@, 1 AB0:0= 2>4K, =8 2 :>5< A;CG05 =5
3@59?D@CB>2K9 A>:), ;CGH5 2A53> 2> 2@5A;5 54K.
7@>A;K5 8 ?>4@>AB:8 A <0AA>9 B5;0 1>;55 50 :3
H5<8G5A:0O 1>;57=L A5@4F0, ?0@>:A87<0;L=0O =0465;C4>G:>20O B0E8:0@48O,
B@5?5B0=85/
<5@F0=85 ?@54A5@489
5:><5=4C5<0O 4>70 A>AB02;O5B 120-480 <3, @0A?@545;5==0O =0 3-4 ?@85<0. 0:A8<0;L=0O
ACB>G=0O 4>70 ?@5?0@0B0 480 <3.
@B5@80;L=0O 38?5@B5=78O
5:><5=4>20==0O ACB>G=0O 4>70 A>AB02;O5B 120-360 <3, @0745;5==0O =0 3 ?@85<0.
!B>9:89 0=B838?5@B5=782=K9 MDD5:B @0728205BAO 2 B5G5=85 =545;8 >B =0G0;0 B5@0?88.
@8 AB5=>:0@488 8 0@8B<88 >1KG=0O 4>70 ?@5?0@0B0 A>AB02;O5B 80 <3 3-4 @070 2 ACB:8 (240-
320 <3).
0:A8<0;L=K9 MDD5:B @0728205BAO, :0: ?@028;>, 2 B5G5=85 48 G0A>2 >B =0G0;0 ;5G5=8O.
0@CH5=85 DC=:F88 ?>G5:
>ABC?=K5 40==K5 >?8A0=> 2 @0745;5 «A>15==>AB8 ?@8<5=5=8O». 0F85=B0< A ?>G5G=>9
=54>AB0B>G=>ABLN 25@0?0<8;0 384@>E;>@84 A;54C5B ?@8<5=OBL A >AB>@>6=>ABLN 8 ?>4
BI0B5;L=K< =01;N45=85
0@CH5=85 DC=:F88 ?5G5=8
?0F85=B>2 A =0@CH5=8O<8 DC=:F88 ?5G5=8 2 7028A8<>AB8 >B AB5?5=8 BO65AB8 459AB285
25@0?0<8;0 384@>E;>@840 CA8;8205BAO 8 C4;8=O5BAO 87-70 70<54;5=8O @0A?040 ;5:0@AB25==>3>
A@54AB20. >MB>7C A;54C5B CAB0=02;820BL A >A>1>9 >AB>@>6=>ABLN 8 =0G8=0BL A<0;KE 4>7
(=0?@8<5@, 4;O ?0F85=B>2 A =0@CH5=8O<8 DC=:F89 ?5G5=8 A=0G0;0 2-3 @070 2 ACB:8 ?> 40 <3,
A>>B25BAB25==> 80-120 <3 2 ACB:8), A15==>AB8 ?@8<5=5=8O».
@8 =5>1E>48<>AB8 =0G0;L=CN 4>7C ?>AB5?5==> ?>2KH0BL 2 7028A8<>AB8 >B A>AB>O=8O
?0F85=B0 8 ;:8=8G5A:>3> >B25B0, :>B>@K9 >F5=8205BAO ?@8 ?@8<5=5=88 ?@5?0@0B0.
*@8 =5>1E>48<>AB8 ?@8<5=5=8O 25@0?0<8;0 2 4>75 40 <3 A;54C5B ?@8<5=OBL ?@5?0@0B A 2>7
<>6=>ABLN B0:>3> 4>78@>20=8O.
5 ?@8=8<0BL ?@5?0@0B 2 ?>;>65=88 ;560.
5@0?0<8;0 384@>E;>@84 =5;L7O =07=0G0BL ?0F85=B0< A 8=D0@:B<<8>:0@40 2 B5G5=85 7 4=59
?>A;5 A>1KB8O.
>A;5 4;8B5;L=>9 B5@0?88 ?@5?0@0B A;54C5B >B<5=8BL, ?>AB5?5==> A=860O 4>7C.
@>4>;68B5;L=>ABL ;5G5=8O >?@545;O5B 2@0G 8=48284C0;L=>, >=0 7028A8B >B A>AB>O=8O
?0F85=B0 8 B5G5=8O 701>;520=8O.

5B8.

5BO< ?@5?0@0B 2 40==>9 ;5:0@AB25==>9 D>@<5 =5 =07=0G0BL.

5@54>78@>2:0.

!878@>2:5 25@0?0<8;0, 7028A0B >B :>;8G5AB20 ?@8=OB>3> ?@5?0@0B0, 2@5<5=8, :>340 1K;8
?@8=OBK 45B>:A8:0F8>==K5 <5@>?@8OB8O, 8 2>7@0AB0 ?0F85=B0.
!8 0@B5@80;L=0O 38?>B5=78O, 1@048:0@48O 4> 0B@8>25=B@8:C;O@=>9 1;>:04K 2KA>:>9 AB5?5=8
8 >AB0=>2:8 A8=CA>2>3> C7;0, 38?5@3;8:5<8O, ABC?>@ 8 <5B01>;8G5A:89 0F84>7. 01;N40;8AL
;5B0;L=K5 A;CG08 2 @57C;LB0B5 ?5@54>78@>2:8.
5G5=85: 4>;6=> 1KBL 3;02=K< >1@07<< ?>445@6820NI8< 8 8=48284C0;L=KCN AB8N 8/8;8
2=CB@825==>5 22545=85 ?@5?0@0B>2 :0;LF8O (:0;LF8O E;>@84) MDD5:B82=> ?@8<5=ONB 4;O
CAB@0=5=8O A8<>2 ?5@54>78@>2:8 ?@8 ?5@>@0;L=>< ?@8<5=5=88 25@0?0<8;0 384@>E;>@840.
A;CG05 7=0G8B5;L=>9 0@B5@80;L=>9 38?>B5=788 8;8 0B@8>25=B@8:C;O@=>9 1;>:04K 2KA>:>9
AB5?5=8 =5>1E>48<> ?@8<5=OBL A@54AB20, ?>2KH0NI85 0@B5@80;L=>5 402;5=85
(A>AC4>AC6820NI85), 8;8 :0@48>AB8@K A>>B25BAB25==>. @8 0A8AB>;88 >4=>2@5<5==> A ?@8
<5=5=85< >1KG=KE <5@>?@8OB89 A;54C5B ?@8<5=8BL β-04@5=5@38G5A:CN AB8N (=0?@8<5@,
87>?@>B5@5=>;0 384@>E;>@84), 4@C385 A@54AB20, =0?@02;5==K5 =0 ?>2KH5=85
0@B5@80;L=>3> 402;5=8O 8;8 ?@>25AB8 2>AAB0=>2;5=85 A5@45G=>9 45OB5;L=>AB8 8 4KE0=8O.

5@0?0<8;0 384@>E;>@84 =5 2K2>48BAO A ?<>ILN 35<>480;870.

>1>G=K5 @50:F88.

15@45G=>-A>AC48AB00 A8AB5<0: AB5=>:0@48O, 0@B5@80;L=0O 38?>B5=78O, A8=>0B@80;L=0O 8

AV-1;>:040 I, II 8;8 III AB5?5=8, 1@048:0@48O, 1@0480@8B<8O A D81@8;;OF859 ?@54A5@489, >AB0=>2:0 A8=CA>2>3> C7;0, 0A8AB>;8O; @8A: >1>AB@5=8O/@0728B8O A5@45G=>9

=54>AB0B>G=>AB8, >@B>AB0B8G5A:85 @50:F88; B0E8:0@48O, 1>;L 70 3@C48=>9, 8=D0@:B <8>:0@40, A5@4F5185=85, ?5@8D5@8G5A:85 >B5:8 ;>4K65.; A8=:>?5, ?@8;82K.

8I520@8B5;L=K9 B@0:B: 48A:>@B 2 682>B5/1>;L, 65;C4>G=>-.8H5G=K5 @0AAB@>9AB20, B0:85 :0: B>H=>B0, @2>B0, <5B5>@87<; 0B>=8O :8H5G=8:0, :8H5G=0O =5?@>E>48<>ABL, 70?>@; ACE>ABL 2> @BC, 38?5@?;078O 45A5= (38=3828B 8 :@>2>B5G5=85).

5@2=0O A8AB5<0: =0@CH5=85 <>73>2>3> :@>2>>1@0I5=8O, A?CB0==>ABL A>7=0=8O, =0@CH5=85 @02=>25A8O, CB><;O5<>ABL, 15AA>==8F0, =5@2>7=>ABL, @>38, ?A8E>7K, =59@>?0B8O, M:AB@0?8@0<84=K9 A8=4@<, A>=;82>ABL, 3>;>2=0O 1>;L, 3>;>2>:@C65=85, ?0@5AB5788, B@5 <>@.

@30=K A;CE0 8 25AB81C;O@=K9 0??0@0B: 72>= 2 CH0E, 25@B83>.

KE0B5;L=0O A8AB5<0, >@30=K 3@C4=>9 ;:5B:8 8 A@54>AB5=8O: 1@>=E>A?07<, 48A?=>M.

>G:8 8 <>G52K45;8B5;L=0O A8AB5<0: ?>G5G=0O =54>AB0B>G=>ABL.

>G5?>;>20O A8AB5<0: M@5:B8;L=0O 48ADC=:F8O, 2 B>< G8A;5 8B5=F8O, G0ABK5

<>G58A?CA:0=8O, =0@CH5=85 <5=AB@C0;L=>3> F8;;0; C ?0F85=B>2 ?>68;>3> 2>7@0AB0 ?@8

4;8B5;L=>9 B5@0?88 @072820;0AL 38=5:<>0AB8O, :>B>@0O ?>;=>ABLN ?@>E>48;0 ?>A;5 >B<5=K ?@5?0@0B0, 30;0:B>@5O.

?>@=>-42830B5;L=0O A8AB5<0: ABL, <80;38O, 0@B@0;38O.

>60 8 ?>4:>6=0O ;:5BG0B:0: AK?L =0 :>65 (2 B>< G8A;5 <0:C;>?0?C;57=0O AK?L, :@0?82=8F0),

>ICI5=85 7C40, 7C4, 0;>?5F8O, 38?5@384@>7, =0@CH5=85 ?83<5=B0F88, 5@8B@><5;0;38O, @<=0O M@8B5<0, A8=4@< !B825=A0-6>=A>=0, >B5: 28=:5, D>B>45@<0B8BK, A8=O:8, ?C@?C@0.

0@CH5=85 >1<5=0 25I5AB2, <5B01>;87<0: 38?5@:0;85<8O.

5?0B>18;80@=0O A8AB5<0: ?>2KH5=85 C@>2=O B@0=A0<8=07, I5;>G=>9 D>AD0B07K 8 18;8@C18=0;

2>7<>6=K ?>@065=85 ?5G5=8 A ;:8=8G5A:8<8 ?@>O2;5=8O<8 (?;>E>5 A0<>GC2AB285, ?>2KH5=85 B5

;L 2 ?@02>< ?>4@515@L5). A2O78 A MB8< F5;5A>>1@07=> ?5@8>48G5A:8 :=B@>;8@>20BL

DC=:F8N ?5G5=8 C ?0F85=B>2. =5:>B>@KE A;CG0OE MB8 87<5=5=8O A0<>AB>OB5;L=> 8AG570NB

?@8 ?@>4>;65=88 B5@0?88.

< A8AB5<0: 38?5@GC2AB28B5;L=>ABL, 0;;5@38G5A:89 35?0B8B, 1@>=E>A?07

@C385: =5G5B:>ABL 7@5=8O, ?>2KH5=85 C@>2=O ?@>;0:B8=0 2 ?;07<5 :@>28, A=865=85

B>;5@0=B=>AB8 : 3;N:>75.

!>>1I0;>AL > ?0@0;8G5 (B5B@0?0@57), 0AA>F88@>20==< A :<18=8@>20==K< ?@8<5=5=85<

25@0?0<8;0 8 :>;E8F8=0. -B> <>65B 1KBL >1CA;>2;5=> ?@>=8=>25=85< :>;E8F8=0 G5@57 35

<0B>M=F5D0;8G5A:89 10@L5@ 2A;54AB285 C3=5B5=8O 25@0?0<8;<< CYP3A4 8 P-qp, ?>MB>

<18=8@>20==>5 ?@8<5=5=85 :>;E8F8=0 8 25@0?0<8;0 =5 @5:<5=4>20=>.

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

#A;>28O E@0=5=8O. >@838=0;L=>9 C?0:>2:5 ?@8 B525 >!

%@0=8BL 2 =54>ABC?=<< 4;O 45B59 <5AB5.

#?0:>2:0. > 10 B01;5B>: 2 1;8AB5@5, ?> 5 1;8AB5@>2 2 ?0G:5.

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

@>872>48B5;L. C1;8G=>5 0:F8>=5@=>5 >1I5AB2> <<0CG=>?@>872>4AB25==K9 F5=B@

<<@I03>2A:89 E8<8:>-D0@<0F52B8G:89 702>4>.

5AB=>0E>645=85 ?@>872>48B5;O 8 53> 04@5A <5AB0 >ACI5AB2;5=8O 45OB5;L=>AB8.

#: @08=0, 03134, 3. □852, C.; 8@0, 17.