

!" #&/

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

"®

(EROTON)

!::04:

4VNG0 @5G>28=0: sildenafil;

1 B01;5B:0 70E, 5:2V20;5=B=8E 50 <3 01> 100 <3 A8;45=0DV;C;

4>?>28=8: :0;LFDVN 3V4@>D>AD0B 483V4@0B, F5;N;>70 :@8AB0;VG=0, :>?>2V4>=, :@5<=VN  
4V>:A84 :>;>W4=89 1572>4=89, B0;L., <03=VN AB50@0B, =0B@VN :@>A:0@<5;>70, :@>E<0;L  
:0@B>?;O=89.

V:0@AL:0 D>@<0. "01;5B:8.

A=>2=V DV78:>-EVABV: B01;5B:8 1V;>3> :>;L>@C, 42>>?C.;V, H5AB83@0==V (D>@<8 «HEXAGON»),  
7 ?>7=0G:>N «\$» 7 >1>E 1>:V2.

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, O:V 70AB>A>2CNBL ?@8 5@5:B8;L=V9 48ADC=:FVW.  
!8;45=0DV;. >4 "% G0403.

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

\$0@<0:>48=0

5E0=V7< 4VW. !8;45=0DV; T ?5@>@0;L=8< ?@5?0@0B<<, I> 70AB>A>2CNBL 4;O ;V:C20==O  
?>@CH5=L 5@5:FVW C G>;>2V:V2. @8 AB0B52>2;NT 7=865=C 5@5:B8;L=C DC=:FVN H;OE<<  
?>A8;5==O ?@8B>:C :@>2V 4> ?5=VA0.

\$V7V>;>3VG=89 <5E0=V7<, I> 7C<>2;NT 5@5:FVN, 2;:NG0T 282V;L=5==O >:8AC 07>BC (NO) C  
:025@=>7=8E BV;0E ?V4 G0A AB0B52>3> 71C465==O. 82V;L=5=89 >:A84 07>BC 0:B82CT D5@<5=B  
3C0=V;0BF8;:07C, I> AB83> 3C0=>78=<>=>D>AD0BC (F\$), I>, C A2>N G5@3C, A?@8G8=OT  
@>7A;01;5==O 3;04:>W 7=8E BV;:, A?@8ONG8 ?@8B>:C :@>2V.

!8;45=0DV; T ?>BC6=8< B0 A5;5:B82=8< V=3V1VB>@<< F\$-A?5F8DVG=>W D>AD>4V5AB5@078 5 (\$5)  
C :025@=>7=8E BV;0E, 45 \$5 2V4?>2V40T 70 @>7?04 F\$. D5:B8 A8;45=0DV;C =0 5@5:FVN<0NBL  
?5@8D5@8G=89 E0@0:B5@. !8;45=0DV; =5 G8=8BL 157?>A5@54=L>W @5;0:ACNG>W 4VW =0  
V7>;L>20=V :025@=>7=V BV;0 ;N48=8, 0;5 ?>BC6=> ?>A8;NT @>7A;01;NNGC 4VN NO =0 40=C  
B:0=8=C. @8 0:B820FVW <5B01>;VG=>3> H;OEC NO/F\$, I> 2V41C20TBLAO ?@8 AB0B52V9 AB8< \$5  
?@872>48BL 4> ?V428I5==O @V2=O F\$ C :025@=>7=8E BV;0E. "0:8< G8=><, 4;O B>3>, I>1 A8;45=0DV;  
A?@8G8=O2 ?>B@V1=89 D0@<0:>;>3VG=89 5D5:B, =5>1EV4=5 AB0B525 71C465==O.

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

1A>@1FVO. !8;45=0DV; H284:> 01A>@1CTBLAO. 0:A8<0;L=V ?;07<>2V :=F5=B@0FVW ?@5?0@0BC  
4>AO30NBLAO ?@>BO3<< 30-120 E28;8= (V7 <54V0=>N 60 E28;8=) ?VA;O 9>3> ?5@>@0;L=>3>  
70AB>AC20==O =0BI5. !5@54=O 01A>;NB=0 1V>4>ABC?=VABL ?VA;O ?5@>@0;L=>3>  
70AB>AC20==O AB0=>28BL 41 % (7 4V0?07>=><< 7=0G5=L 2V4 25 4> 63 %). # @5:><5=4>20=>=V 4>7  
(2V4 25 4> 100 <3) ?>:07=8:8 AUC B0 !<sub>max</sub> A8;45=0DV;C ?VA;O 9>3> ?5@>@0;L=>3> 70AB>AC20==O  
?V428ICNBLAO ?@>?>@FV9=> 4> 4>78.

@8 70AB>AC20==V A8;45=0DV;C ?V4 G0A ?@89>@1FVW 7=86CTBLAO V7 A5@54=V< ?>4>265==O< T  
max 4> 60 E28;8= V A5@54=V< 7=865==O< C<sub>max</sub> =0 29 %.

>7?>4V;. !5@54=V9 @V2=>206=89 >1T< @>7?>4V;C (V<sub>d</sub>) AB0=>28BL 105 ;VB@V2, I> A2V4G8BL ?@>  
@>7?>4V; ?@5?0@0BC C B:0=8=0E >@30=V74=>:@0B=>3> ?5@>@0;L=>3> 70AB>AC20==O  
A8;45=0DV;C 2 4>7V 100 <3 A5@54=O <0:A8<0;L=0 7030;L=0 ?;07<>20 :=F5=B@0FVO A8;45=0DV;C  
AB0=>28BL ?@81;87=> 440 =3/<; (:>5DVFVT=B 20@V0FVW AB0=>28BL 40 %). A:V;L:8 7207C20==O  
A8;45=0DV;C B0 9>3> 3>;>2=>3> N-45A<5B8;<5B01>;VBC 7 1V;:0<8 ?;07<8 4>AO30T 96 %, A5@54=O  
<0:A8<0;L=0 ?;07<>20 :=F5=B@0FVO 2V;L=>3> A8;45=0DV;C 4>AO30T 18 =3<; (38 =<>;L). !BC?V=L  
7207C20==O 7 1V;:0<8 ?;07<8 :@>2V =5 70;568BL 2V4 7030;L=8E :=F5=B@0FV9 A8;45=0DV;C.  
# 74>@>28E 4>1@>2>;LFDV2, O:V 70AB>A>2C20;8 A8;45=0DV; >4=>:@0B=> C 4>7V 100 <3, G5@57  
90 E28;8= 2 5O:C;OBV 287=0G0;>AO <5=H5 0,0002 % (C A5@54=L>A>20=>W 4>78.

V>B@0=AD>@<0FVO. 5B01>;V7< A8;45=0DV;C 74V9A=NTBLAO 3>;>2=8< G8=>< 7 CG0ABN A>

<0;L=8E V7>D5@<5=BV2 ?5GV=:8 CYP3A4 (3>;>2=89 H;OE) B0 CYP2C9 (4@C3>@O4=89 H;OE).  
>;>2=89 F8@:C;NNG89 <5B01>;VB CB2>@NTBLAO H;OE>< N-45<5B8;N20==O A8;45=0DV;C.  
15;5:B82=VABL<5B01>;VBC 2V4=>A=> \$5 ?>@V2=O==O 7 A5;5:B82=VABN A8;45=0DV;C, 0  
0:B82=VABL<5B01>;VBC 2V4=>A=> \$5 AB0=>28BL ?@81;87=> 50 % 0:B82=>ABV ?>G0B:>2>W  
@5G>28=8. ;07<2V :=F5=B@0FVW FL>3> <5B01>;VBC AB0=>2;OBL ?@81;87=> 40 %  
:=F5=B@0FVW A8;45=0DV;C C ?;072V. N-45<5B8;L>20=89 <5B01>;VB 707=0T ?>40;LH>3> <5B01>;V7  
4 9>3> =0?V2282545==O AB0=>28BL ?@81;87=> 4 3>48=8.  
;V 030;L=89 ;V@5=A A8;45=0DV;C AB0=>28BL 41 ;/3>4, 7C>2;NNG8 ?5@V>4 9>3> =0?V2282545==O  
B@820;VABN 3-5 3>48=. /: ?VA;O ?5@>@0;L=>3>, B0: V ?VA;O 2=CB@VH=L>25==>3> 70AB>AC20==O  
5:A:@5FVO A8;45=0DV;C C 283;O4V<5B01>;V BV2 74V9A=NTBLAO 3>;>2=8< G8=>< V7 :0;<  
(?@81;87=> 80 % 70AB>A>20=>W ?5@>@0;L=>W 4>78) B0 <5=H>N N 7 A5G5N (?@81;87=> 13 %  
70AB>A>20=>W ?5@>@0;L=>W 4>78).

\$0@<0.:V=5B8:0 2 >A>1;828E 3@C? ?0FVT=BV2.

0FVT=B8 ;VB=L>3> 2V:C. # 74>@>28E 4>1@>2>;L FV2 ;VB=L>3> 2V:C (2V:< 2V4 65 @>:V2)  
2V47=0G0;>AO 7=865==O ;V@5=AC A8;45=0DV;C, I> 7C<>2;N20;> ?V428I5==O ?;07<28E  
:=F5=B@0FV9 A8;45=0DV;C B0 9>3> 0:B82=>3> N-45<5B8;L>20=>3> <5B01>;VBC ?@81;87=> =0 90 %  
?>@V2=O=> 7 2V4?>2V4=8<8 :=F5=B@0FVO<8 C 74>@>28E 4>1@>2>;L FV2 <>;>4H>3> 2V:C (18-45  
@>:V2). # 7207:C 7 2V:>28<8 2V4ABO<8 C 7207C20==V 7 1V;:0<8 ?;07<8 :@>2V 2V4?>2V4=5  
?V428I5==O ?;07<2>W :=F5=B@0FVW 2V;L=>3> A8;45=0DV;C AB0=>28;> ?@81;87=> 40%.

8@:>20 =54>AB0B=VABL. # 4>1@>2>;L FV2 V7 ?>@CH5==O<8 DC=:FVW =8@>: ;53:>3> B0 ?>3>  
ABC?5=O (;V@5=A :@50B8=V=C 30-80 <;/E2) D0@<0.:V=5B8:0 A8;45=0DV;C 70;8H0;0AO =57N ?VA;O  
9>3> >4=>:@0B=>3> ?5@>@0;L=>3> 70AB>AC20==O C 4>7V 50 <3. !5@54=V AUC B0 C<sub>max</sub> N-45  
<5B8;L>20=>3> <5B01>;VBC ?V428IC20;8AO =0 126 % B0 73 % 2V4?>2V4=> ?>@V2=O=> 7 B0:8<8  
?>:07=8:0<8 C 4>1@>2>;L FV2 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FVW =8@>:.. 4=0: G5@57 28A>:C  
V=482V4C0;L=C 20@V015;L=VABL FV 2V4ABV =5 1C;8 AB0B8AB8G=> 7=0GCI8<8. # 4>1@>2>;L FV2  
V7 B06:8<8 ?>@CH5==O<8 DC=:FVW =8@>: (;V@5=A :@50B8=V=C =86G5 30 <;/E2) ;V@5=A  
A8;45=0DV;C 7=86C202AO, I> ?@872>48;> 4> A5@54=VE ?V428I5=L AUC B0 C<sub>max</sub> =0 100 % B0 88 %  
2V4?>2V4=> ?>@V2=O=> V7 4>1@>2>;LFO<8 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FVW =8@>:.. @V<  
B>3>, 7=0G5==O AUC B0 C<sub>max</sub> N-45<5B8;L>20=>3> <5B01>;VBC 7=0GCI5 ?V428IC20;8AO =0 79 % B0  
200 % 2V4?>2V4=>.

5GV=:>20 =54>AB0B=VABL. # 4>1@>2>;L FV2 V7 F8@>7< ?5GV=:8 ;53:>3> B0 ?>3> ABC?5=O (;0AV2  
B0 70 ;:0A8DV:0FVTN '09;40-N) ;V@5=A A8;45=0DV;C 7=86C202AO, I> ?@872>48;> 4> ?V428I5==O  
AUC (84 %) B0 C<sub>max</sub> (47 %) ?>@V2=O=> 7 4>1@>2>;LFO<8 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FV9  
?5GV=:8. \$0@<0.:V=5B8:0 A8;45=0DV;C C ?0FVT=BV2 V7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 B06:>3>  
ABC?5=O =5 282G0;0AO.

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

>:070==O.

@5?0@0B @5:><5=4CTBLAO 70AB>A>2C20B8 G>;>2V:0< 7 5@5:B8;L=>N 48ADC=:FVTN, O:0  
287=0G0TBLAO O: =5740B=VABL 4>AO3B8 01> ?V4B@8<0B8 5@5:FVN AB0B52>3> G;5=0,  
=5>1EV4=C 4;O CA?VH=>3> AB0B52>3> 0:BC.

;O 5D5:B82=>W 4VW ?@5?0@0BC =5>1EV4=5 AB0B525 71C465==O.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> A8;45=0DV;C 01> 1C4L-O:>W 7 4>?>28= ?@5?0@0BC; >4=>G0A=5  
70AB>AC20==O V7 4>=>@0<8 >:A84C 07>BC (B0:8<8 O: 0 =VB@0B0<8 C 1C4L-O:V9 D>@B8?>:070=5,  
>A:V;L:8 2V4<>, I> A8;45=0DV;<0T 2?;82 =0 H;OE8 <5B01>;V7:A84C 07>BC/F8;;VG=>3> 3C0=>78=  
<=>D>AD0BC (F\$) B0 ?>B5=FNVT 3V?>B5=782=89 5D5:B =VB@0BV2; AB0=8, ?@8 O:8E AB0B520  
0:B82=VABL T =51060=>N (B06:V A5@F52>-AC48==V @>7;048, B0:V O: =5AB01V;L=0 AB5=>:0@4VO  
01> A5@F520 =54>AB0B=VABL B06:>3> ABC?5=O).

@89>< ?@5?0@0BC ?@>B8?>:070=89 ?0FVT=B0<, O:V 2B@0B8;8 7V@ =0 >4=>FV 2=0A;V4>:  
=50@B5@V0;L=>W ?5@54=>W VH5W =59@>?0BVW 7>@>2>3> =5@20 =570;56=> 2V4 B>3>, ?>2'  
070=0 FO ?0B>;>3VO V7 ?>?5@54=V< 70AB>AC20==O< V=3V1VB>@V2 \$5 G8 =V.

002=VABL B0:8E 70E2>@N20=L O: ?>@CH5==O DC=:FVW ?5GV=:8 B06:>3> ABC?5=O,  
0@B5@V0;L=0 3V?>B5=7VO (0@B5@V0;L=89 B8A: =86G5 90/50 << @B. AB.), =5I>402=> ?5@5=5A5=89

V=AC;LB 01> V=D0@:B :0@40 B0 2V4>2V 4535=5@0B82=V 70E2>@N20==O AVB:V2:8, B0:V O: ?V3  
<5=B=89 @5B8=VB (=525;8:0 :V;L:VABL B0:8E ?0FVT=BV2<0T 35=5B8G=V @>7;048  
D>AD>4V5AB5@07 AVB:V2:8), >A:V;L:8 157?5:0 A8;45=0DV;C =5 4>A;V46C20;0AO C B0:8E  
?V43@C?0E ?0FVT=BV2.

**70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.**

D5:B8 V=H8E ;V:0@AL:8E 70A>1V2 =0 A8;45=0DV;.

>A;V465==O *in vitro*. 5B01>;V7< A8;45=0DV;C 2V41C20TBLAO ?5@5206=> 7 CG0ABN V7>D>@<8 34  
(3>;>2=89 H;OE) B0 V7>D>@<8 2!9 (4@C3>@O4=89 H;OE) F8B>E@>@8 F8E V7>D5@<5=BV2 <>6CBL  
7=86C20B8 ;;V@5=A A8;45=0DV;C, 0 V=4C:B>@8 F8E V7>D5@<5=BV2 <>6CBL ?V428IC20B8 ;;V@5=A  
A8;45=0DV;C.

>A;V465==O *in vivo*. >?C;OFV9=89 D0@<0:V=5B8G=89 0=0;V7 40=8E ;;V=VG=8E 4>A;V465=L ?@>45  
<=>AB@C202 7=865==O ;;V@5=AC A8;45=0DV;C ?@8 9>3> >4=>G0A=>AC20==V 7 V=3V1VB>@0<8  
CYP3A4 (B0:8<8 O: :5B>:>=07>;, 5@8B@>AC20==V A8;45=0DV;C B0 V=3V1VB>@V2 CYP3A4  
7@>AB0==O G0AB>B8 ?>1VG=8E O28I =5 A?>AB5@V30;>AO, A;V4 @>73;O=CB8 <>6;82VABL  
70AB>AC20==O ?>G0B:>2>W 4>78 A8;45=0DV;C 25<3.

4=>G0A=5 70AB>AC20==O V=3V1VB>@C -?@>B5078 @8B>=02V@C, 4C65 ?>BC6=>3> V=3V1VB>@C  
450, C AB0=V @V2=>206=>W :=F5=B@0FVW (500<3 1 @07 =0 4>1C) B0 A8;45=0DV;C (@07>20 4>70  
100 <3) ?@872>48;> 4> ?V428I5==O C<sub>max</sub> A8;45=0DV;C =0 300% (C 4 @078) B0 ?V428I5==O ?;07<>2>W  
AUC A8;45=0DV;C =0 1000% (C 11 @07V2). '5@57 24 3>48=8 ?;07<>2V @V2=V A8;45=0DV;C 2A5 I5  
AB0=>28;8 ?@81;87=> 200 =3/<; ?>@V2=O=> 7 @V2=5< ?@81;87=> 5 =3/<;, E0@0:B5@=8< 4;O  
70AB>AC20==O A8;45=0DV;C >:@5<>, I> 2V4?>2V40T 7=0G=>=02V@C =0 H8@>:89 A?5:B@  
AC1AB@0BV2 450. !8;45=0DV; =5 2?;820T =0 D0@<0:V=5B8:C @8B>=02V@C. >3;O4C =0 FV D0@  
<0:V=5B8G=V 40=V >4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 @8B>=02V@C =5 @5:>  
<5=4CTBLAO (482. @>74V; «A>1;82>ABV 70AB>AC20==O»); C 1C4L-O:>

4=>G0A=5 70AB>AC20==O V=3V1VB>@C -?@>B5078 A0:2V=02V@C, V=3V1VB>@C CYP3A4, C 4>7V,  
I> 70157?5GCT @V2=>206=C :=F5=B@0FVN (1200<3 3 @078 =0 4>1C), B0 A8;45=0DV;C (100<3  
@07>2>) ?@872>48;> 4> ?V428I5==O C<sub>max</sub> A8;45=0DV;C =0 140% B0 71V;LH5==O A8AB5<=>W  
5:A?>78FVW (AUC) A8;45=0DV;C =0 210%. 5 28O2;5=> 2?;82C A8;45=0DV;C =0 D0@<0:V=5B8:C  
A0:2V=02V@C (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»). 5@5410G0TBLAO, I> 1V;LH  
?>BC6=V V=3V1VB>@8 CYP3A4, B0:V O: :5B>:>=07>; B0 VB@0:>=07>;, 1C4CBL <0B8 1V;LH  
28@065=89 2?;82.

@8 70AB>AC20==V A8;45=0DV;C (100<3 @07>2>) B0 5@8B@>3> V=3V1VB>@C CYP3A4, C  
@V2=>206=>max, T<sub>max</sub>, :=AB0=BC H284:>ABV 5;V40;LH89 ?5@V>4 =0?V2282545==O A8;45=0DV;C  
01> 9>3> 3>;>2=>3> F8@:C;NNG>3> <5B01>;VBC. &8<5B848= (V=3V1VB>@ F8B>E@>@ CYP3A4) C  
4>7V 800 <3 ?@8 >4=>G0A=>AC20==V V7 A8;45=0DV;C < C 4>7V 50 <3 C 74>@>28E 4>1@>2>;LFV2  
?@872>482 4> ?V428I5==O ?;07<>28E :=F5=B@0FV9 A8;45=0DV;C =0 56%.

@59?D@CB>289 AV: T A;01:8 V=3V1VB>@<< CYP3A4 C ABV=FV :8H5G=8:C V <>65 A?@8G8=8B8 ?>  
2V.

4=>:@0B=5 70AB>AC20==O 0=B0F84V2 (<03=VN 3V4@>:A84C/0;N:A84C) =5 2?;820;> =0  
1V>4>ABC?=VABL A8;45=0DV;C.

%>G0 4>A;V465=L A?5F8DVG=>W 270T<>4VW 7 CAV<0 ;V:0@AL:8<8 70A>10<8 =5 ?@>2>48;>AO, 70  
40=8<8 ?>?C;OFV9=>3> D0@<0:V=5B8G=>3> 0=0;V7C, D0@<0:V=5B8:0 A8;45=0DV;C =5 73>  
>4=>G0A=>AC20==V V7 ;V:0@AL:8<8 70A>10<8, I> =0;560BL 4> 3@C?8 V=3V1VB>@V2 CYP2C9  
(B>;1CB0

4=>G0A=5 70AB>AC20==O 0=B03>=VAB0 5=4>B5;V=C 1>A5=B0=C (?>@ CYP3A4, CYP2C9 B0,  
<>6;82>, CYP2C19) C @V2=>206=>max A8;45=0DV;C =0 62,6% B0 55,4 % 2V4?>2V4=>. ">4=>G0A=5  
70AB>AC20==O B0:8E ?>BC6=8E V=4C:B>@V2 CYP3A4 O: @8D065 ?@872>48B8 4> 1V;LH  
28@065=>3> 7=865==O :=F5=B@0FVW A8;45=0DV;C 2 ?;072V.

V:>@0=48; O2;OT A>1>N 3V1@84 0:B820B>@0 :0;LFV28E :0=0;V2 B0 =VB@0BC. VB@0B=89 :=5=B  
7C<>2;NT <>6;82VABL 9>3> A5@9>7=>W 270T<>4VW 7 A8;45=0DV;C>

D5:B8 A8;45=0DV;C =0 V=HV ;V:0@AL:V 70A>18.

>A;V465==O *in vitro*. !8;45=0DV; A;01:89 V=3V1VB>@ V7>D>@< 12, 2C9, 2C19, 2D6, 2E1 B0 34  
F8B>E@>50 > 150

V4ACB=V 40=V I>4> 270T<>4VW A8;45=0DV;C B0 B0:8E =5A?5F8DVG=8E V=3V1VB>@V2  
D>AD>4V5AB5@078, O: B5>DV;V= B0 48?V@840<>;  
>A;V465==O *in vivo*. A;V;L:8 2V4<>, I> A8;45=0DV; <0T 2?;82 =0 <5B01>;V7<>:A84C 07>BC  
/F8;;VG=>3> 3C0=>78=<=>D>AD0BC (F\$), 1C;> 2AB0=>2;5=>, I> A8;45=0DV; ?>B5= FVNT  
3V?>B5=782=C 4VN =VB@0BV2, B>3> >4=>G0A=5 70AB>AC20==O 7 4=>=>@0<8 >:A84C 07>BC 01> 7  
=VB@0B0<8 C 1C4L-O:V9 D>@B8?>:070=5 (482. @>74V; «@>B8?>:070==O»).

4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 1;>:0B>@V2 α-04@5=>@5F5?B>@V2<>65 ?@8725AB8 4>  
@>728B:C A8<0B8G=>W 0@B5@V0;L=>W 3V?>B5=7VW C 450:8E AE8;L=8E 4> FL>3> ?0FVT= BV2.  
"0:0 @50:FVO =09G0ABVH5 28=8:0;0 ?@>BO3<< 4 3>48= ?VA;O 70AB>AC20==O A8;45=0DV;C (482.  
@>74V; «!>AV1 70AB>AC20==O B0 4>78» B0 «A>1;82>ABV 70AB>AC20==O»). # E>4V 4>A;V465=L  
A?5F8DVG=>W 270T<>4VW ;V:0@AL:8E 70A>1V2 1;>:0B>@ α-04@5=>@5F5?B>@V2 4>:A07>78= (4  
<3 B0 8 <3) B0 A8;45=0DV; (25<3, 50 <3 B0 100 <3) 70AB>A>2C20;8 >4=>G0A=> ?0FVT=B0< V7  
4>1@>O:VA=>N 3V?5@?;07VTN ?5@542>W 70;>78, AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0  
?@8 70AB>AC20==V 4>:A07>78=C. # F8E ?>?C;OFVOE A?>AB5@V30;>AO A5@54=T 4>40B:>25  
7=865==O 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 =0 7/7 << @B. AB., 9/5 << @B. AB. B0 8/4 <<  
@B. AB. B0 A5@54=T 7=865==O 0@B5@V0;L=>3> B8A:C C ?>;>65==V AB>OG8 =0 6/6 << @B. AB., 11/4  
<< @B. AB., 4/5 << @B. AB. 2V4?>2V4=>. @8 >4=>G0A=>AC20==V A8;45=0DV;C B0 4>:A07>78=C C  
?0FVT= BV2, AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0 ?@8 70AB>AC20==V 4>:A07>78=C, V=>4V  
?>2V4<>;O;>AO ?@> @>728B>: A8<0B8G=>W >@B>AB0B8G=>W 3V?>B5=7VW. # F8E ?>2V4>  
<;5==OE 9H;>AO ?@> 28?04:8 70?0<>@>G5==O B0 AB0= ?5@54 =5?@8B<=VABN, 0;5 157 A8=:>?5  
5 A?>AB5@V30;>AO 6>4=8E 7=0GCI8E 270T<>4V9 ?@8 >4=>G0A=>AC20==V A8;45=0DV;C (50<3) V  
B>;1CB0  
!8;45=0DV; (50<3) =5 ?@872>482 4> ?>4>265==O G0AC :@>2>B5GV, A?@8G8=5=>W 70AB>AC20==O<  
0F5B8;A0;VF8;>2>W :8A;>B8 (150 <3).  
!8;45=0DV; (50<3) =5 ?>B5= FVN202 3V?>B5=782=C 4VN 0;>3>;N C 74>@>28E 4>1@>2>;LFV2 ?@8  
A5@54=VE <0:A8<0;L=8E @V2=OE 5B0=>;C :@>2V 80 <3/4;  
# ?0FVT= BV2, O:V 70AB>A>2C20;8 A8;45=0DV;; =5 A?>AB5@V30;>AO 6>4=8E 2V4AB59 ?@>DV;N  
?>1VG=8E 5D5:BV2 ?>@V2=O=> ? ?;0F51> ?@8 >4=>G0A=>AC20==V B0:8E ;:0AV2 3V?>B5=782=8E  
;V:0@AL:8E 70A>1V2 O: 4VC@5B8:8, 1;>:0B>@8 β-04@5=>@5F5?B>@V2, V=3V1VB>@8 \$,  
0=B03>=VAB8 0=3V>B5=78=C, 0=B83V?5@B5=782=V ;V:0@AL:V 70A>18 (AC48=>@>7H8@N20;L=V  
B0 F5=B@0;L=>W 4VW), 1;>:0B>@8 04@5=5@3VG=8E =59@=>V2, 1;>:0B>@8 :0;LFVT28E :0=0;V2 B0  
1;>:0B>@8 α-04@5=>@5F5?B>@V2. # A?5FV0;L=>A;V465==V 270T<>4VW ?@8 >4=>G0A=>AC20==V  
A8;45=0DV;C (100<3) B0 0<;>48?V=C ?0FVT=B0< 7 0@B5@V0;L=>N 3V?5@B5=7VTN  
A?>AB5@V30;>AO 4>40B:>25 7=865==O A8AB>;VG=>3> 0@B5@V0;L=>3> B8A:C 2 ?>;>65==V ;560G8  
=0 8 << @B. AB. V4?>2V4=5 7=865==O 4V0AB>;VG=>3> 0@B5@V0;L=>3> B8A:C AB0=>28;> 7 <<  
@B. AB. 0 25;8G8=>N FV 4>40B:>2V 7=865==O 0@B5@V0;L=>3> B8A:C 1C;8 ?>@V2=O==8<8 V7 B8<8,  
I> A?>AB5@V30;8AO ?@8 70AB>AC20==V ;8H5 A8;45=0DV;C C 74>@>28E 4>1@>2>;LFV2 (482.  
@>74V; «\$0@<0;>;>3VG=V 2;0AB82>ABV»).

!8;45=0DV; C 4>7V 100 <3 =5 2?;8202 =0 D0@<0>:V=5B8G=V ?>:07=8:8 V=3V1VB>@V2 -?@>B5078,  
A0:2V=02V@C B0 @8B>=02V@C, I> T AC1AB@0B0<8 CYP3A4.  
# 74>@>28E 4>1@>2>;LFV2 G>;>2VG>W AB0BV 70AB>AC20==O A8;45=0DV;C C @V2=>206=>max  
1>A5=B0=C (125 <3 2 @078 =0 4>1C) =0 49,8 % 42 % 2V4?>2V4=>.

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

> ?>G0B:C B5@0?VW A;V4 7V1@0B8 <548G=89 0=0<=57 ?0FVT=B0 B0 ?@>25AB8 DV78:0;L=5  
>1AB565==O 4;O 4V03=>AB8:8 5@5:B8;L=>W 48ADC=:FVW B0 287=0G5==O WW <>6;828E ?@8G8=  
\$0:B>@8 @878:C A5@F52>-AC48==8E 70E2>@N20=L. A;V;L:8 AB0B520 0:B82=VABL  
AC?@>2>46CTBLAO ?52=8< @878:<< 7 1>:C A5@FO, 4> ?>G0B:C 1C4L-O:>3> ;V:C20==O  
5@5:B8;L=>W 48ADC=:FVW ;V:0@<0T >FV=8B8 AB0= A5@F52>-AC48==>W A8AB5<8 ?0FVT=B0.  
!8;45=0DV; G8=8BL AC48=>@>7H8@N20;L=C 4VN, I> ?@>O2;OTBLAO ;53:8< B0 :>@>B:>G0A=8<  
7=865==O< 0@B5@V0;L=>3> B8A:C (482. @>74V; «\$0@<0>48=0 ?@87=0G5==O A8;45=0DV;C ;V:0@  
<0T @5B5;L=> 72068B8, G8 <>65 B0:89 5D5:B =5A?@8OB;82> 2?;820B8 =0 ?0FVT= BV2 V7 ?52=8<8  
>A=>2=8<8 70E2>@N20==O<8, >A>1;82> C :<<1V=0FVW 7V AB0B52>N 0:B82=VABN. > ?0FVT= BV2  
V7 ?V428I5=>N GCB;82VABN 4> 207>48;0B0B>@V2 =0;560BL ?0FVT=B8 7 >1AB@C:FVTN 282V4=>3>  
B@0:BC ;V2>3> H;C=>G:0 (=0?@8;:04, AB5=>7 0>@B8, 3V?5@B@>DVG=0 >1AB@C:B82=0 :0@4V>

?0BVO) 01> ?0FVT=B8 7 @V4:VA=8< A8=4@<<<  
@5?0@0B ?>B5= FVNT 3V?>B5=782=89 5D5:B =VB@0BV2 (482. @>74V; <<@>B8?>:070==O»).

# ?>AB<0@:5B8=3>2>4V ?>2V4<<;O;>AO ?@> BO6:V ?>1VG=V @50:FVW 7 1>:C A5@F52>-AC48==>W  
A8AB5<8, 2::NG0NG8 V=D0@:B :0@40, =5AB01V;L=C AB5=>:0@4VN, @0?B>2C A5@F52C A<5@BL,  
H;C=>G:>2C 0@8B20A:C;O@=V :@>2>28;828, B@0=78B>@=C VH5B5=7VN, I> 70 G0A>< 71V30;8AO  
V7 70AB>AC20==O< A8;45=0DV;C. # 1V;LH>ABV ?0FVT=BV2, 0;5 =5 C 2AVE, VA=C20;8 D0:B>@8  
@878:C A5@F52>-AC48==8E 70E2>@N20=L. 030B> B0:8E ?>1VG=8E @50:FV9 A?>AB5@V30;>AO ?V4  
G0A 01> >4@07C ?VA;O AB0B52>3> 0:BC V ;8H5 :V;L:0 B@0?8;>AO =524>27V ?VA;O 70AB>AC20==O  
A8;45=0DV;C 157 AB0B52>W 0:B82=>ABV. ">  
@V0?V70A>18 4;O ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW, C B>15@56=VABN ?0FVT=B0< 7 0=0B><0  
01> ;59:5  
VA;O 28E>4C A8;45=0DV;C =0 @8=>: ?>2V4<<;O;>AO ?@> 28?04:8 ?>4>265=>W 5@5:FVW B0 ?@V0?V7  
5@5:FVO B@820T 4>2H5 =V6 4 3>48=, ?0FVT=B0< A;V4 =5309=> 725@=CB8AO 70 <548G=>N 4>?>  
<>3>N. # @07V 2V4ACB=>ABV =5309=>3> ;V:C20==O ?@V0?V7< <>65 ?@8725AB8 4> ?>H:>465==O  
B:0=8= ?5=VA0 B0 4> ABV9:>W 2B@0B8 ?>B5= FVW.  
4=>G0A=5 70AB>AC20==O 7 V=H8<8 V=3V1VB>@0<8 \$5 01> V=H8<8 ?@5?0@0B0<8 4;O ;V:C20==O  
5@5:B8;L=>W 48ADC=:FVW. 57?5:C B0 5D5:B82=VABL >4=>G0A=>3> 70AB>AC20==O A8;45=0DV;C 7  
V=H8<8 V=3V1VB>@0<8 \$5 01> V=H8<8 ?@5?0@0B0<8 4;O ;V:C20==O 3V?5@B5=7VW ;535=52>W  
0@B5@VW, I>), G8 7 V=H8<8 ?@5?0@0B0<8 4;O ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW =5 282G0;8.  
>AC20==O B0:8E :<1V=0FV9 =5 @5:><5=4>20=5.  
?;82 =0 7V@. !?>=B0==V ?>2V4<<;5==O ?@> 28=8:=5==O 45D5:BV2 7>@C =04E>48;8 0A>FV9>20=> V7  
70AB>AC20==O< A8;45=0DV;C B0 V=H8E V=3V1VB>@V2 \$5 (482. @>74V; <<1VG=V @50:FVW»).

@> 28?04:8 =50@B5@V0;L=>W ?5@54=L>W VH5W =52@>?0BVW 7>@>2>3> =5@20, I> T @V4:VA=8<  
AB0=><, =04E>48;8 A?>=B0==V ?>2V4<<;5==O B0 ?>2V4<<;O;>AO C =03;O4>2>A;V465==V  
0A>FV9>20=> V7 70AB>AC20==O< A8;45=0DV;C B0 V=H8E V=3V1VB>@V2 \$5 (482. @>74V; <<1VG=V  
@50:FVW»).

0FVT=BV2 A;V4 ?>?5@548B8, I> C @07V @0?B>2>3> ?>@CH5==O 7>@C  
70AB>A>2C20==O A8;45=0DV;C A;V4 ?@8?8=8B8 B0 =5309=> 725@=CB8AO 4> ;V:0@O (482. @>74V;  
<<@>B8?>:070==O»).

4=>G0A=5 70AB>AC20==O 7 @8B>=02V@>4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0  
@8B>=02V@C =5 @5:><5=4CTBLAO (482. @>74V; <<70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0  
V=HV 2848 270T<>4V9»).

4=>G0A=5 70AB>AC20==O 7 I;:>.0B>@0<8 α-04@5=>@5F5?B>@V2. 0FVT=B0<, O:V 70AB>A>2CNBL  
1;:>.0B>@8 α-04@5=>@5F5?B>@V2, 70AB>A>2C20B8 A8;45=0DV; A;V4 7 >15@56=VABN, >A;V;L:8  
B0:0 :<1V=0FVO <>65 ?@8725AB8 4> A8<0B8G=>W 0@B5@V0;L=>W 3V?>B5=7VW C 450:8E  
AE8;L=8E 4> FL>3> ?0FVT=BV2. !8<0B8G=0 0@B5@V0;L=0 3V?>B5=7VO 70728G09 28=8:0T ?@>B03>  
< 4 3>48= ?VA;O 70AB>AC20==O A8;45=0DV;C.<5B>N O28 A8@B>AB0B8G=>W 3V?>B5=7VW.  
?;82 =0 :@>2>B5GV. >A;V465==O B@><1>F8BV2 ;N48=8 ?@>45<=>=AB@C20;8, I> in vitro A8;45=0DV;  
>?B5= FVNT 0=B803@530FV9=V 5D5:B8 =0B@VN =VB@>?@CA84C. 5<0T 6>4=>W V=D>@<0FVW  
I>4> 157?5:8 70AB>AC20==O A8;45=0DV;C ?0FVT=B0< V7 ?>@CH5==O<8 73>@B0==O :@>2V 01>  
>3>AB@>N ?5?B8G=>N 28@07:>N. "0:8< G8=><, 70AB>AC20==O A8;45=0DV;C ?0FVT=B0<8 FVTW  
3@C?8 <>6;825 ;8H5 ?VA;O @5B5;L=>W >FV=:8 A?V22V4=>H5==O :>@8ABV B0 @878:V2.  
VA;O 70AB>AC20==O 4>78 100<3 74>@>28< 4>1@>2>;LFO< =5 A?>AB5@V30;>AO 2?;82C =0  
<>@D>;>3VN G8 @CE>  
B@0B0 A;CEC. V:0@O< A;V4 ?>@048B8 ?0FVT=B0< ?@8?8=8B8 70AB>AC20==O V=3V1VB>@V2 \$5,  
2::NG0NG8 ?@5?0@0B, B0 =5309=> 725@=CB8AO 70 <548G=>3> 4>?><>3>N C 28?04:0E @0?B>2>3>  
7=865==O G8 2B@0B8 A;CEC. @> FV O28I0, I> B0:>6 <>6CBL AC?@>2>46C20B8AO 472>=< C 2CE0E  
B0 70?0<>@>G5==O<, ?>2V4<<;O;>AO 7 0A>FV0FVTN C G0AV V7 70AB>AC20==O< V=3V1VB>@V2  
\$5, 2::NG0NG8 ?@5?0@0B. 87=0G8B8, G8 FV O28I0 ?@O<> ?>2O70=V V7 70AB>AC20==O<  
V=3V1VB>@V2 \$5, G8 7 V=H8<8 D0:B>@0<8, =5<>6;82>.  
4=>G0A=5 70AB>AC20==O V7 3V?>B5=782=8<8 ?@5?0@0B0<8. @5?0@0B G8=8BL A8AB5<=C  
AC48=>@>7H8@N20;L=C 4VN B0 <>65 C ?>40;LH>A>2CNBL 3V?>B5=782=V ;V:0@AL:V 70A>18. #  
>:@5<>A;V465==V ;V:0@AL:>W 270T<>4VW >4=>G0A=5 70AB>AC20==O 0<;>48?V=C (5 <3 01> 10 <3)  
B0 A8;45=0DV;C(100 <3) ?5@>@0;L=> A?>AB5@V30;>AO A5@54=T 4>40B:>25 7=865==O  
A8AB>;VG=>3> B8A:C =0 8 << @B. AB. B0 4V0AB>;VG=>3> =0 7 << @B. AB.

0E2>@N20==O, I> ?5@540NBLAO AB0B528< H;OE> 0AB>AC20==O A8;45=0DV;C=5 70E8I0T 2V4  
70E2>@N20=L, I> ?5@540NBLAO AB0B528< H;OE>73;O=CB8 <>6;82VABL ?@>V=AB@C:BC20B8  
?0FVT=BV2 I>4> =5>1EV4=8E 70?>1V6=8E 70A>1V2 4;O 70E8ABC 2V4 70E2>@N20=L, I>  
?5@540NBLAO AB0B528< H;OE><, 2;:NG0NG8 2V@CA V45DVF8BC ;N48=8.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.  
@5?0@0B =5 ?@87=0G5=89 4;O 70AB>AC20==O 6V=:0

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> 7 V=H8<8  
<5E0=V7<0<8.  
>A;V465=L 2?;82C ?@5?0@0BC =0 740B=VABL :5@C20B8 B@0=A?>@B=8<8 70A>10<8 B0 ?@0FN20B8  
7 V=H8<8 <5E0=V7<0<8 =5 ?@>2>48;8. A:V;L:8 C E>4V ;:V=VG=8E 4>A;V465=L 70AB>AC20==O  
A8;45=0DV;C ?>2V4<;O;>AO ?@> 28?04:8 70?0<>@>G5==O B0 ?>@CH5==O 7 1>:C >@30=V2 7>@C,  
?5@54 B8< O: AV40B8 70 :5@<> B@0=A?>@B=>3> 70A>1C 01> ?@0FN20B8 7 <5E0=V7<0<8, ?0FVT=B0  
< =5>1EV4=> 70AC20B8, O:>N T WE=O V=482V4C0;L=0 @50:FVO =0 70AB>AC20==O ?@5?0@0BC.

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

@5?0@0B 70AB>A>2C20B8 ?5@>@0;L=>.

>@>A;V. 5:<5=4>20=0 4>70 ?@5?0@0BC AB0=>28BL 50 <3, 70AB>A>2C20B8 C @07V  
=5>1EV4=>ABV ?@81;87=> 70 1 3>48=C 4> AB0B52>W 0:B82=>ABV. 0;56=> 2V4 5D5:B82=>ABV B0  
?5@5=>A8<>ABV ?@5?0@0BC 4>7C <>6=0 71V;LH8B8 4> 100 <3 01> 7<5=H8B8 4> 25 <3. 0:A8<0;L=0  
@5:<5=4>20=0 4>70 AB0=>28BL 100 <3. '0AB>B0 70AB>AC20==O <0:A8<0;L=>W @5:<5=4>20=>W  
4>78 ?@5?0@0BC AB0=>28BL 1 @07 =0 4>1C. @8 70AB>AC20==V ?@5?0@0BC ?V4 G0A ?@89>  
0FVT=B8 ;VB=L>3> 2V:C. 5>1EV4=VABL C :>@5:FVW 4>78 ?0FVT=B0< ;VB=L>3> 2V:C (≥ 65 @>:V2)  
2V4ACB=O.

0FVT=B8 V7 =8@:>2>N =54>AB0B=VABN. 0FVT=B0< V7 =8@:>2>N =54>AB0B=VABN ;53:>3> B0 ?>3>  
ABC?5=O B06:>ABV (:;V@5=A :@50B8=V=C 30-80<;E2) @5:<5=4>20=0 4>70 ?@5?0@0BC T B0:>N 6,  
O: =02545=> 28I5 C @>74V;V «□>@>A;V».

A:V;L:8 C ?0FVT=BV2 V7 =8@:>2>N =54>AB0B=VABN B06:>3> ABC?5=O (:;V@5=A :@50B8=V=C <30  
<;E2) ;:V@5=A A8;45=0DV;C 7=865=89, A;V4 @>73;O=CB8<>6;82VABL 70AB>AC20==O 4>78 25<3.  
0;56=> 2V4 5D5:B82=>ABV B0 ?5@5=>A8<>ABV ?@5?0@0BC ?@8 =5>1EV4=>ABV 4>7C <>6=0  
71V;LH8B8 ?>ABC?>2> 4> 50 <3 B0 4> 100 <3.

0FVT=B8 V7 ?5GV=:>2>N =54>AB0B=VABN. A:V;L:8 C ?0FVT=BV2 V7 ?5GV=:>2>N =54>AB0B=VABN  
(=0?@8::04, F8@>7<);:V@5=A A8;45=0DV;C 7=865=89, A;V4 @>73;O=CB8<>6;82VABL  
70AB>AC20==O 4>78 25 <3. 0;56=> 2V4 5D5:B82=>ABV B0 ?5@5=>A8<>ABV ?@5?0@0BC ?@8  
=5>1EV4=>ABV 4>7C <>6=0 71V;LH8B8 ?>ABC?>2> 4> 50 <3 B0 4> 100 <3.

0FVT=B8, O:V 70AB>A>2CNBL V=HV ;V:0@AL:V 70A>18. /:I> ?0FVT=B8 >4=>G0A=> 70AB>A>2CNBL  
V=3V1VB>@8 CYP3A4 (482. @>74V; «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848  
270T<>4V9»), A;V4 @>73;O=CB8 <>6;82VABL 70AB>AC20==O ?>G0B:>2>W 4>78 25<3 (70 28=OB:<<  
@8B>=02V@C, 70AB>AC20==O O:>3> >4=>G0A=> V7 A8;45=0DV;< =5 @5:<5=4CTBLAO, 482.  
@>74V; «A>1;82>ABV 70AB>AC20==O»).

<5B>N «A>1;82>ABV 70AB>AC20==O» B0 «□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV  
2848 270T<>4V9»).

@8 ?@87=0G5==V A8;45=0DV;C C 4>7V 25 <3 70AB>A>2C20B8 ?@5?0@0B C 2V4?>2V4=>7C20==V  
01> ;V:0@AL:V9 D>@

VB8. @5?0@0B =5 ?>:070=89 4> 70AB>AC20==O >A>10< 2V:< 4> 18 @>:V2.

5@54>7C20==O.

V4 G0A 70AB>AC20==O @07>2>W 4>78 A8;45=0DV;C 4> 800<3 ?>1VG=V @50:FVW 1C;8 ?>4V1=8<8  
4> B8E, I> A?>AB5@V30;8AO ?@8 70AB>AC20==V A8;45=0DV;C C =86G8E 4>70E, 0;5  
7CAB@VG0;8AO G0ABVH5 B0 1C;8 1V;LH B06:8<8. 0AB>A>2C20==O A8;45=0DV;C C 4>7V 200<3 =5  
?@872>48;> 4> ?V428I5==O 5D5:B82=>ABV, 0;5 A?@8G8=O;> 7@>AB0==O :V;L:>ABV 28?04:V2  
@>728B:C ?>1VG=8E @50:FV9 (3;>2=>3> 1>;N, ?@8?;82V2, 70?0<>@>G5==O, 48A?5?AVW,  
70::045=>ABV =>A0, ?>@CH5=L 7 1>:C >@30=V2 7>@C).

# @07V ?5@54>7C20==O ?@8 =5>1EV4=>ABV A;V4 24020B8AO 4> 728G09=8E ?V4B@84V2.  
@8A:>@5==O ;V@5=AC A8;45=0DV;C ?@8 35<>4V0;V7V <0;>9<>2V@=5 2=0A;V4>: 28A>:>3>  
ABC?5=O 7207C20==O ?@5?0@0BC 7 1V;:0<8 ?;07<8 :@>2V B0 2V4ACB=>ABV 5;V

>1VG=V @50:FVW.

09G0ABVH5 ?>2V4><;O;>AO ?@> B0:V ?>1VG=V @50:FVW O: 3>;>2=89 1V;L, ?@8?;828, 48A?5?AVO,  
70;:045=VABL =>A0, 1V;L C A?8=V, 70?@>@>G5==O, =C4>B0, ?@8?;828 60@C, ?>@CH5==O 7>@C,  
FV0=>?AVO B0 70BC<0=5==O 7>@C.

#AV ;V=VG=> 7=0GCIV ?>1VG=V @50:FVW, I> A?>AB5@V30;8AO ?V4 G0A ;V=VG=8E 4>A;V465=L  
G0ABVH5, =V6 ?@8 70AB>AC20==V ?;0F51>, =02545=> =86G5 2V4?>2V4=> 4> ;:0A8DV:0FVW <18AB5  
<0->@30=-;:0A» B0 G0AB>B8: 4C65 G0AB> (≥ 1/10), G0AB> (≥ 1/100 - < 1/10), =5G0AB> (≥ 1000 - < 1  
/100) B0 @V4:> (≥ 1/10000 - < 1/1000). @V< B>3>, G0AB>B0 ;V=VG=> 7=0GCIV ?>1VG=8E @50:FV9,  
?@> O:V ?>2V4><;O;>AO C @0A2V4C 70AB>AC20==O ?VA;O 28E>4C =0 @8=>:, 287=0G5=0 O: =52V4>  
<0. # <560E :>6=>W G0AB>B=>W 3@C?8 ?>1VG=V @50:FVW =02545=V C ?>@O4:C 7<5=H5==O WE  
A5@9>7=>ABV.

=D5:FV9=V B0 V=20782=V 70E2>@N20==O.

5G0AB>: @8=VB.

1>:C VW A8AB5<8.

5G0AB>: 3V?5@GCB;82VABL.

1>:C =5@2>2>W A8AB5<8.

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

'0AB>: 70?0<>@>G5==O.

5G0AB>: A>;82VABL, 3V?5AB57VO.

V4:>: V=AC;LB, B@0=78B>@=0 VH5<8\*, @5F84828 AC4<\*, A8=>?5.

1>:C >@30=V2 7>@C.

'0AB>: ?>@CH5==O A?@89=OBBO :>;L>@V2\*\*, @>7;048 7>@C, 70BC<0=5==O 7>@C.

5G0AB>: @>7;048 A;L>7>284V;5==O\*\*\*, 1V;L 2 >G0E, D>B>D>1VO, D>B>?AVO, 3V?5@G59,

OA:@02VABL 7>@C, :=N=:B82VB.

V4:>: =50@B5@V0;L=0 ?5@54=O VH5?0BVO 7>@>2>3> =5@20\*, >;N7VO AC48= AVB:V2:8\*,  
@5B8=0;L=89 :@>2>28;82, 0@B5@V>A;;5@>B8G=0 @5B8=>?0BVO, ?>@CH5==O 7 1>:C AVB:V2:8,  
3;0C:><0, 45D5:B8 ?>;O 7>@C, 48?;>?VO, 7=865==O 3>AB@>B8 7>@C, ?VO, 0AB5=>?VO, ?;020NGV ?>  
284=>3> BV;0, ?>@CH5==O 7 1>:C @094C6=>W >1>;>=:8, O20 AONG8E :@C3V2 =02:>;> 465@5;0  
A2VB;0 (30;>) C ?>;V 7>@C, =01@O: >G59, ?@8?CE;VABL >G59, ?>@CH5==O 7 1>:C >G59, 3V?5@5  
=N=:B828, ?>4@07=5==O >G59, 0=><0;L=V 2V4GCBBO 2 >G0E, =01@O: ?>2V;:, 7=510@2;5==O A;;5@8.  
1>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC.

5G0AB>: 25@B83>, 472V= C 2CE0E.

V4:>: 3;CE>B0.

1>:C A5@FO.

5G0AB>: B0EV:0@4VO, ?>A8;5=5 A5@F518BBO.

V4:>: @0?B>20 A5@F520 A<5@BL\*, V=D0@:B :0@40, H;C=>G:>20 0@8B:0@4VO.

1>:C AC48=.

'0AB>: ?@8?;828 :@>2V 4> >1;8GGO, ?@8;828 60@C.

5G0AB>: 0@B5@V0;L=0 3V?5@B5=7VO/3V?>B5=7VO.

1>:C @5A?V@0B>@=>W A8AB5<8, 3@C4=>W ;:VB:8 B0 A5@54>ABV==O.

'0AB>: 70;:045=VABL =>A0.

5G0AB>: =>A>20 :@>2>B5G0, 70;:045=VABL ?@840B:>28E ?07CE =>A0.

V4:>: 2V4GCBBO AB8A=5==O C 3>@;V, =01@O: A;87>2>W >1>;>=:8 =>A0, ACEVABL C =>AV.

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

'0AB>: =C4>B0, 48A?5?AVO.

5G0AB>: 30AB@>57>D0350;L=0 @5D;N:A=0 E2>@>10, 1;N20==O, 1V;L C 25@E=V9 G0AB8=V 682>B0,  
ACEVABL C @>BV.

V4:>: 3V?5AB57VO @>B>2>W ?>@>6=8=8.

1>:C H:V@8 B0 ?V4H:V@=>W B:0=8=8.

5G0AB>: 28A8?0==O.

V4:>: A8=4@< !BV25=A0-6=>A>=0\*, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7\*.

1>:C >?>@=>-@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8.

5G0AB>:

1>:C A5G>284V;L=>W A8AB5<8.

5G0AB>: 35<0BC@VO.

1>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7.

V4>: :@>2>B5G0 7V AB0B52>3> G;5=0, ?@V0?V7<\*, 35<0B>A?5@4>265=0 5@5:FVO.

030;L=V @>7;048.

5G0AB>: 1V;L C 3@C4OE, ?V428I5=0 2B<;N20=VABL, 2V4GCBBO 60@C.

V4>: ?>4@07=5==O.

1AB565==O.

5G0AB>: ?V428I5=0 G0AB>B0 A5@F528E A:>@>G5=L.

\* >2V4><;O;>AO ;8H5 ?V4 G0A 4>A;V465==O ?VA;O 28E>4C ?@5?0@0BC =0 @8=>:.

\*\* >@CH5==O A?@89=OBBO :>;L>@C: E;>@>?AVO, E@<0B>?AVO, FV0=>?AVO, 5@8B@>?AVO, :A0=B>?AVO.

\*\*\* >@CH5==O A;L>7>284V;5==O: ACEVABL 2 >G0E, ?>@CH5==O A;L>7>284V;5==O B0 ?V428I5==O A;L>7>284V;5==O.

86G5707=0G5=V O28I0 A?>AB5@V30;8AO C < 2 % ?0FVT=BV2; ?@8G8==89 270T<>7207>: =5

287=0G5=89. >2V4><;5==O 2::NG0;8 O28I0, I> <0;8 2V@>3V4=89 7207>: V7 70AB>AC20==O<

?@5?0@0BC. /28I0, O:V =5 1C;8 707=0G5=V, 1C;8 ;53:8<8 B0 ?>2V4><;5==O 1C;8 4C65 =5B>G=8<8, I>1 <0B8 7=0G5==O.

030;L=V. 01@O: >1;8GGO, @50:FVW D>B>GCB;82>ABV, H>:, 0AB5=VO, 1V;L, @0?B>25 ?04V==O, 1V;L C 682>BV, @0?B>25 ?>H:>465==O.

I>:C A5@F52>-AC48==>W A8AB5<8: AB5=>:0@4VO, V-1;>:040, ABC@0;L=0 3V?>B5=7VO, VH5

:0@40, B@><1>7 AC48= 3>;>2=>3> <>7:C, @0?B>20 7C?8=:0 A5@FO, ?>@CH5==O @57C;LB0BV2 =0, :0@4V>?0BVO.

I>:C H;C=:>2>:8H:>2>3> B@0:BC: 3;>A8B, :>;VB, 48AD03VO, 30AB@8B, 30AB@>5=B5@8B, 57>D03VB, AB<0B8B, ?>@CH5==O @57C;LB0BV2 ?5GV=:>28E ?@>1, @5:B0;L=0 :@>2>B5G0, 3V=3V2VB.

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

I>:C <5B01>;V7A?@030, =01@O:, ?>403@0, =5AB01V;L=89 4V015B, 3V?5@3;V:53;V:5

I>:C A:5;5B=>-<O7>2>W A8AB5<8: 0@B@8B, 0@B@>7, @>7@82 ACE>68;;O, B5=>A8=>2VB, 1V;L C :VAB:0E, 2VB.

I>:C =5@2>2>W A8AB5<8: 0B0:AVO, =52@0;3VO, =59@>?0BVO, ?0@5AB57VO, B@5<>@, 25@B83>, 45?@5AVO, 157A>==O, 0=<0;L=V A=>284V==O, 7=865==O @5D;5:AV2.

I>:C 48E0;L=>W A8AB5<8: 0AB<0, 48A?=>5, ;0@8=3VB, D0@8=3VB, A8=CA8B, 1@>=EVB, ?>A8;5=5 A;8=>284V;5==O, ?>A8;5==O :0H;N.

I>:C H:V@8: :@>?82O=:0, 35@?5A, A25@1V6, ?VB;82VABL, 28@07:8 H:V@8, :=B0:B=89 45@<0B8B, 5:AD>;V0B82=89 45@<0B8B.

!?5F8DVG=V 2V4GCBBO: @0?B>25 7=865==O G8 2B@0B0 A;CEC, 1V;L C 2CE0E, :@>2>28;82 C >:, :0B0@0:B0, ACEVABL 2 >G0E.

I>:C C@>35=VB0;L=>W A8AB5<8: F8AB8B, =V:BC@VO, ?V428I5=0 G0AB>B0 A5G>28?CA:0=L, 71V;LH5==O <>;>G=8E 70;>7, =5B@8<0==O A5GV, ?>@CH5==O 5O:C;OFVW, =01@O: AB0B528E

>@30=V2, 0=>@307

>A2V4 70AB>AC20==O ?VA;O 28E>4C =0 @8=>: VA;O 28E>4C A8;45=0DV;C =0 @8=>: 1C;8

V45=B8DV:>20=V =86G5707=0G5=V ?>1VG=V @50:FVW. A:V;L:8 ?@> B0:V @50:FVW ?>2V4<;ONBL 4>1@>2V;L=> B0 ?>2V4<;5==O =04E>4OBL C =52V4>ABV, =5 702648 <>6=0 4>AB>2V@=> >FV=8B8

WE G0AB>BC B0 2AB0=>28B8 ?@8G8==89 7207>: 7 5:A?>78FVTN ;V:0@AL:>3> 70A>1C. &V O28I0 1C;8 707=0G5=V O: G5@57 WE A5@9>7=VABL, G0AB>BC ?>2V4<;5==O, 2V4ACB=VABL GVB:>3>

0;LB5@=0B82=>3> 7207:C, B0: V G5@57 :<1V=0FVN F8E D0:B>@V2.

!5@F52>-AC48==V B0 F5@51@>20A:C;O@=V O28I0. >2V4><;O;>AO ?@> A5@9>7=V A5@F52>-

AC48==V, F5@51@>20A:C;O@=V B0 AC48==V O28I0, 2::NG0NG8 F5@51@>20A:C;O@=C :@>2>B5GC, AC10@0E=>W40;L=C B0 2=CB@VH=L>F5@51@0;L=C :@>2>B5GC B0 ;535=52C :@>2>B5GC, I> 1C;8

?>2O70=V 2 G0AV V7 70AB>AC20==O< A8;45=0DV;C. V;LHVABL ?0FVT=BV2, 0;5 =5 2AV<0;8

VA=CNGV D0:B>@8 A5@F52>-AC48==>3> @878:C. >2V4<;O;>AO, I> 1030B> 7 F8E O28I 28=8::8 ?V4 G0A 01> >4@07C ?VA;O AB0B52>W 0:B82=>ABV, B0 45:V;L:0 O28I 28=8::8 2V4@07C ?V4 G0A



70AB>AC20==O A8;45=0DV;C157 A5:AC0;L=>W 0:B82=>ABV. =HV O28I0 28=8::8 ?@>BO3×  
=0ABC?=8E 3>48= G8 4=V2 ?VA;O 70AB>AC20==O A8;45=0DV;C B0 AB0B52>W 0:B82=>ABV. 5>6;82>  
2AB0=>28B8, G8 <0NBL FV O28I0 ?@O<89 72O7>: V7 70AB>AC20==O< ?@5?0@0BC, 7V AB0B52>N  
0:B82=VABN, 7 =0O2=8<8 D0:B>@0<8 @878:C G8 V7 :<1V=0FVTN F8E D0:B>@V2, G8 7 V=H8<8  
D0:B>@0<8.

@>2>=>A=0 B0 ;V 207>>.:N782=89 :@87. # =525;8:> ?@8?8=5=>A;V465==V 70AB>AC20==O  
?@5?0@0BC 520F8> (A8;45=0DV; ) 4;O ?0FVT=BV2 7 ;535=52>N 0@B5@V0;L=>N 3V?5@B5=7VTN,  
2B>@8==>N I>4> A5@?>?>4V1=>.;VB8==>W 0=5AC20==V A8;45=0DV;C ?@> @>728B>:  
207>>.:N782=8E :@87V2, I> ?>B@51C20;8 3>A?VB0;V70FVW, ?>2V4<;O;>AO G0ABVH5, =V6 ?@8  
70AB>A>2C20==V ?;0F51>. ;V=VG=5 7=0G5==O FVTW V=D>@<0FVW 4;O ?0FVT=BV2, O:V  
70AB>A>2CNBL A8;45=0DV;C 7<5B>N ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW, T =52V4<8  
5@2>20 A8AB5<0: B@82>6=VABL, B@0=78B>@=0 3;>10;L=0 0<=57VO.  
! ?5F8DVG=V 2V4GCBBO.

!;CE. VA;O 28E>4C ?@5?0@0BC =0 @8=>: ?>2V4<;O;>AO ?@> 28?04:8 @0?B>2>3> 7=865==O G8  
2B@0B8 A;CEC, ?>2O70=V C G0AV V7 70AB>AC20==O< A8;45=0DV;C. # 450:8E 28?04:0E ?>2V4<  
<;O;>AO ?@> =0O2=VABL<548G=8E AB0=V2 B0 V=H8E D0:B>@V2, I> <>3;8 2V4V3@0B8 @>;L C  
@>728B:C ?>1VG=8E @50:FV9 7 1>:C A;CEC. # 1030BL>E 28?04:0E V=D>@<0FVO I>4> ?>40;LH>3>  
<548G=>3> A?>AB5@565==O 2V4ACB=O. 87=0G8B8, G8 FV O28I0 ?@O<> ?>2O70=V V7  
70AB>AC20==O< ?@5?0@0BC A8;45=0DV;C, 7 =0O2=8<8 D0:B>@0<8 @878:C 2B@0B8 A;CEC, 7 :>  
<1V=0FVTN F8E D0:B>@V2 G8 7 V=H8<8 D0:B>@0<8, =5<>6;82>.

V@: B820 2B@0B0 7>@C, ?>G5@2>=V==O >G59, ?5GV==O 2 >G0E, ?V428I5==O 2=CB@VH=L>>G=>3>  
B8A:C, =01@O: AVB:V2:8, AC48==V 70E2>@N20==O AVB:V2:8 G8 :@>2>B5G0, 2V4H0@C20==O  
A:;>?>4V1=>3> BV;0.

VA;O 28E>4C ?@5?0@0BC =0 @8=>: @V4:> ?>2V4<;O;>AO ?@> 28?04:8 =50@B5@V0;L=>W  
?5@54=L>W VH5W =52@>?0BVW 7>@>2>3> =5@20, I> T ?@8G8=>N 7=865==O 7>@C, 2:;NG0NG8  
?>ABV9=C 2B@0BC 7>@C, O:V 1C;8 ?>2O70=V C G0AV V7 70AB>AC20==O< V=3V1VB>@V2 \$5,  
2:;NG0NG8 A8;45=0DV;C. 030B> 7 ?0FVT=BV2, 0;5 =5 2AV,<0;8 =0O2=V 0=0B> AC48==V D0:B>@8  
@878:C @>728B:C =50@B5@V0;L=>W ?5@54=L>W VH5W =52@>?0BVW 7>@>2>3> =5@20,  
2:;NG0NG8 (0;5 =5>1>2O7:>2> >1<56CNG8AL) B0:V: =87L:5 A?V22V4=>H5==O 4V0<5B@0 5:A:020FVW  
B0 48A:C 7>@>2>3> =5@20 (70ABV9=89 48A: 7>@>2>3> =5@20), 2V: 2V4 50 @>:V2, 0@B5@V0;L=0  
3V?5@B5=7VO, 70E2>@N20==O :>@>=0@=8E 0@B5@V9, 3V?5@;V?V45

2VBC20==O ?@> ?V4>7@N20=V ?>1VG=V @50:FVW. 2VBC20==O ?@> ?V4>7@N20=V ?>1VG=V  
@50:FVW ?VA;O @5TAB@0FVW ;V:0@AL:>3> 70A>1C<0T 206;825 7=0G5==O. &5 40T 7<3C  
?@>2>48B8 157?5@5@2=89 <=>VB>@8=3 A?V22V4=>H5==O @8ABN V @878:0<8, ?>2O70=8<8 V7  
70AB>AC20==O< FL>3> ;V:0@AL:>3> 70A>1C. V:0@O< A;V4 72VBC20B8 ?@> 1C4L-O:V  
?V4>7@N20=V ?>1VG=V @50:FVW 2V4?>2V4=> 4> 28<>3 70:>=>402AB20.

"5@ABV. 4 @>:8.

#<>28 715@V30==O.

15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B5>!.  
15@V30B8 C =54>ABC?=>

#?0:>2:0.

"01;5B:8 ?> 50 <3, ?> 100 <3 1 (1E1), 2 (2E1), 4 (4E1) C 1;VAB5@V, C ?0GFV.

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

0 @5F5?B><.

8@>1=8:.

" <<\$VB>D0@

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.

#:@0W=0, 84500, >=5FL:0 >1;.,