

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

\$□#□®
(FLUNOL®)

!;:04:

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

1 :0?AC;0 =07>;C 50 <3;

4>?>28=8: ;0:B>78 <=>3V4@0B, :@>E<0;L :C:C@C47O=89, :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89,
<03=VN AB50@0B, =0B@VN ;0C@8;AC;LD0B;

:0?AC;0 65;0B8=>20 B25@40: 65;0B8=, B8B0=C 4V>:A84 (171), V=483>:0@

V:0@AL:0 D>@<0. □0?AC;8.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 3 7 :@8H5G:>N A8=L>3> :>;L>@C B0 :>@?CA>
< 1V;>3> :>;L>@C, I>4=>@V4=89 ?>@>H>: 1V;>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0.

@>B83@81:>2V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O, ?>EV4=V B@807>;C. >4 "% J02A C01.

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

\$0@<0:>48=0

\$.C:>=07>; O2;OT A>1>N 0:B82=C @5G>28=C 3@C?8 B@807>;C. 0 @0EC=>: ?>BC6=>3> V=3V1C20==O
D5@<5=BC 14α-45<5B8;078 3@81:>2>W ;VB8=8 2V= ?@83=VGCT A8=B57 5@3>AB5@>;C, >A=>2=>3>
:>=5=B0 <5<1@0= ;VB8= 3@81V2 V ?;VA=O28. '8=8BL DC=3VAB0B8G=C 4VN V T 0:B82=8 2V4=>A=>

G8A5;L=8E ?0B>35==8E 3@81V2, B0:8E O: *Candida spp.* (*C.albicans*, *C. tropicalis*), *Cryptococcus*
neoformans, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenkii*,
Paracoccidioides brasiliensis, *C. glabrata* B0 1V;LH>ABV 45@<0B>DVBV2. \$.C:>=07>; <5=H 0:B82=89
2V4=>A=> *spargillus spp.* *B0 enicillium marneffeii*, =5 4VT =0 3@818 *C. krusei*, *Fussarium spp.* B0 783>

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

\$.C:>=07>; 4>1@5 01A>@1CTBLAO ?VA;O ?5@>@0;L=>3> ?@89>3> 1V>4>ABC?=VABL ?5@528ICT 90
%. 8H5 11-12 % D;C:>=07>;C 7207CNBLAO 7 1V;:0<8 ?;07<8 :@>2V. 1T< @>7?>4V;C ?@81;87=> B0:89
A0<89, O: V >1T< @>7?>4V;C 2>48 2 >@30=V7=07>; 4>1@5 ?@>=8:0T 2 CAV @V48=8 >@30=V7@. 0:A8
<0;L=V @V2=V 22V 4>AO30NBLAO ?@>B03>< 0,5-1,5 3>48=8, 1V>;>3VG=89 ?5@V>4=0?V2@>7?04C
AB0=>28BL <0965 30 3>48= (I> T ?V4AB02>N 4;O >4=>@07>2>3> 70AB>AC20==O ?@5?0@0BC C
;V:C20==V 203V=0;L=>3> :0=484>7C; 70 2AV<0 V=H8<8 ?>:070==O<8 D;C:>=07>; 70AB>A>2C20B8 1
@07 =0 4>1C). 5=H5 5 % D;C:>=07>;C <5B01>;V7CTBLAO ?V4 G0A ?5@H>3> ?@>E>465==O G5@57
?5GV=:C. @81;87=> 80 % D;C:>=07>;C =5 707=0T <5B01>;V748BLAO =8@:0<8, 70;8H>: 282>48BLAO C
283;04V <5B01>;VBV2.

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

>:070==O.

V:C20==O B0:8E 70E2>@N20=L C 4>@>A;8E O::

:@8?B>:>:289 <5=V=3VB;

:>:F84i>W4>7;

V=20782=V :0=484>78;

:0=484>78 A;87>28E >1>;>=:, 2;;NG0NG8 :0=484>7 @>B>3>;B:8 B0 :0=484>7 AB@02>E>4C,

:0=484C@VO, E@>=VG=89 :0=484>7 H:V@8 V A;87>28E >1>;>=:;

E@>=VG=89 0B@>DVG=89 :0=484>7 (:0=484>7, A?@8G8=5=89 28:>@8AB0==O< 7C1=8E ?@>B57V2)

?@8 =55D5:B82=>ABV <0B>;>3VG=8E 3V3VT=VG=8E 70A>1V2;

203V=0;L=89 :0=484>7, 3>AB@89 G8 @5F8482CNG89, :>;8 @5G=>N;

:0=484>7=89 10;0=VB, :>;8 @5G=>N;

45@<0B>78, 2;;NG0NG8 7 AB>?, 7 3;045=L:>W H:V@8, ?0E>289 45@<0B>7, @V7=>10@2=89 ;8H09 B0

:0=484>7=V V=D5:FVW H:V@8, :>;8 A8AB5<=0 B5@0?VO =5 T 4>@5G=>N;

45@<0B>DVB=89 >=VE>7, :>;8 70AB>AC20==O V=H8E ;V:0@AL:8E 70A>1V2 =5 T 4>@5G=8

@>DV;0:B8:0 B0:8E 70E2>@N20=L C 4>@>A;8E O::

@5F8482 :@8?B>:>:>2>3> <5=V=3VBC C ?0FVT=BV2 7 28A>:8< @878:>< 9>3> @>728B:C;
@5F8482 :0=484>7C @>B>3;>B:8 01> AB@02>E>4C C ?0FVT=BV2 7 7 28A>:8< @878:>< 9>3>
@>728B:C;
7=865==O G0AB>B8 @5F8482V2 203V=0;L=>3> :0=484>7C (4 01> 1V;LH5 28?04:8 =0 @V:);
?@>DV;0:B8:0 :0=484>7=8E V=D5:FV9 C ?0FVT=BV2 V7 B@820;>N =59B@>?5=VTN (=0?@8::04,
?0FVT=BV2 7V 7;>O:VA=8<8 70E2>@N20==O<8 :@>2V, O:V >B@8B5@0?VN G8 ?0FVT=BV2 ?@8
B@0=A?;0=B0FVW 35<>?>5B8G=8E AB>21C@>28E :;VB8=).

VB8.
0AB>A>2C20B8 ;V:0@AL:89 70AV1 C D>@@VW ?0FVT=BV2 <>6=0 B>4V, :;>8 4VB8 740B=V 157?5G=>
?@>:>2B=CB8 :0?AC;C, I> 70728G09 T <>6;828< C 2VfV 2V4 5 @>:V2.
\$;C=>;® <>6=0 70AB>A>2C20B8 4VBO< 4;O ;V:C20==O :0=484>7V2 A;87>28E >1>;>=: (:0=484>7
@>B>3;>B:8, :0=484>7 AB@02>E>4C), V=20782=8E :0=484>7V2, :@8?B>:>:>2>3> <5=V=3VBC B0 4;O
?@>DV;0:B8:8 :0=484>7=8E V=D5:FV9 C ?0FVT=BV2 7V 7=865=8< V?5@5465==O @5F8482C
:@8?B>:>:>2>3> <5=V=3VBC C 4VB59 V7 28A>:8< @878:>< 9>3> @>728B:C.
"5@0?VN ?@5?0@0B>< \$;C=>;® <>6=0 @>7?>G8=0B8 4> >B@8<0==O @57C;LB0BV2 :C;LBC@0;L=8E
B0 V=H8E ;01>@0B>@=8E 4>A;V465=L; ?VA;O >B@8<0==O @57C;LB0BV2 0=B810:B5@V0;L=C
B5@0?VN A;V4 A:>@83C20B8 2V4?>2V4=8< G8=>

@>B8?>:070==O.

V?5@GCB;82VABL 4> D;C:>=07>;C, 4> V=H8E 07>;L=8E A?>;C:01> 4> 1C4L-O:>W 7 4>?>28=
?@5?0@0BC.
4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 B5@D5=048=C ?0FVT=B0<, O:V 70AB>A>2CNBL
D;C:>=07>; 1030B>@07>2> C 4>70E 400 <3/4>1C B0 28I5 (73V4=> 7 @57C;LB0B0<8 4>A;V465==O 270T
<>4VW 1030B>@07>2>3> 70AB>AC20==O).
4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 V=H8E ;V:0@AL:8E 70A>1V2, I> ?>4>26CNBL V=B5@20;
QT B0 <5B01>;V7CNBLAO 70 4>?><>3>N D5@<5=BC CYP34 (=0?@8::04 F870?@84C, 0AB5;C, ?V
<>784C, EV=V48=C B0 5@8B@>

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

@>B8?>:070=> ACAC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2.
&870?@84. >2V4><;O;>AO ?@> @>728B>: ?>1VG=8E @50:FV9 7 1>:C A5@FO, C B> ?0@>:A87<0;L=C
H;C=>G:>2C B0EV:0@4VN B8?C «?V@C5B» C ?0FVT=BV2, O:V >4=>G0A=> 70AB>A>2C20;8
D;C:>=07>; B0 F870?@84. >=B@>;L>20=5 4>A;V465==O ?@>45<=>AB@C20;>; I> >4=>G0A=5
70AB>AC20==O 200 <3 D;C:>=07>;C 1 @07 =0 4>1C B0 20 <3 F870?@84C 4 @078 =0 4>1C ?@872>48;>
4> 7=0G=>3> ?V428I5==O @V2=O F870?@84C C ?;072V B0 4> ?>4>265==O V=B5@20;C QT. 4=>G0A=5
70AB>AC20==O D;C:>=07>;C B0 F870?@84C ?@>B8?>:070=5.
"5@D5=048=. '5@57 28?04:8 @>728B:C B06:8E A5@F528E 0@8B4>265==O< V=B5@20;C QTc, C
?0FVT=BV2, O:V 70AB>A>2CNBL 07>;L=V ?@>B83@81:>2V ;V:0@AL:V 70A>18 >4=>G0A=> 7
B5@D5=048=><, 1C;8 ?@>2545=V 4>A;V465==O 270T<>4VW F8E ?@5?0@0BV2. # E>4V 4>A;V465==O
?@8 70AB>AC20==V D;C:>=07>;C C 4>7V 200 <3 =0 4>1C =5 1C;> 28O2;5=> ?>4>265==O V=B5@20;C
QTc. =H5 4>A;V465==O ?@8 70AB>AC20==V D;C:>=07>;C C 4>70E 400 <3 B0 800 <3 =0 4>1C ?@>45
<=>AB@C20;>; I> 70AB>AC20==O D;C:>=07>;C C 4>70E 400 <3 =0 4>1C 01> 28I5 7=0G=> ?V428ICT
@V25=L B5@D5=048=C C ?;072V ?@8 >4=>G0A=>AC20==V F8E ?@5?0@0BV2. !CAC20==O
D;C:>=07>;C C 4>70E 400 <3 01> 28I5 7 B5@D5=048=>< ?@>B8?>:070=5. @8 70AB>AC20==V
D;C:>=07>;C C 4>70E =86G5 400 <3 =0 4>1C >4=>G0A=> 7 B5@D5=048=>< A;V4 ?@>2>48B8
@5B5;L=89 <=>VB>@8=3 AB0=C ?0FVT=B0.

AB5; !CAC20==O D;C:>=07>;C B0 0AB5;C <>65 7=878B8 ;;V@5=A 0AB5;C. !?@8G8=5=5 F8<
?V428I5==O :>=F5=B@0FVW 0AB5;C C ?;072V <>65 ?@8725AB8 4> ?>4>265==O V=B5@20;C QT B0 C
@V4:VA=8E 28?04:0E 4> ?0@>:A87<0;L=>W H;C=>G:>2>W B0EV:0@4VW B8?C «?V@C5B». 4=>G0A=5
70AB>AC20==O D;C:>=07>;C B0 0AB5;C ?@>B8?>:070=5.

V<>784 B0 EV=V48=. !CAC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C <>65 ?@872>48B8 4>
?@83=VG5==O <5B01>;V7in vitro B0 in vivo =5 ?@>2>48;8. V428I5==O :>=F5=B@0FVW ?V<>784C 01>
EV=V48=C C ?;072V <>65 A?@8G8=OB8 ?>4>265==O V=B5@20;C QT B0 C @V4:VA=8E 28?04:0E
?@872>48B8 4> @>728B:C ?0@>:A87<0;L=>W H;C=>G:>2>W B0EV:0@4VW B8?C «?V@C5B». 4=>G0A=5
70AB>AC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C ?@>B8?>:070=5.

@8B@> 4=>G0A=5 70AB>AC20==O 5@8B@>=07>;C ?>B5=FV9=> <>65 ?@872>48B8 4> ?V428I5==O @878:C @>728B:C :0@4V>B>:A8G=>ABV (?>4>265==O V=B5@20;C QT, ?0@>:A87<0;L=0 H;C=>G:>20 B0EV:0@4VO B8?C «?V@C5B») B0, O: =0A;V4>:, 4> @0?B>2>W A5@F52>W A<5@BV. 0AB>AC20==O :><1V=0FVW 40=8E ;V:0@AL:8E 70A>1V2 ?@>B8?>:070=5.
5 @5:><5=4CTBLAO >4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2.
0;>D0=B@8=. \$;C:>=07>; <>65 A?@8G8=8B8 ?V428I5==O :>=F5=B@0FVW 30;>D0=B@8=C C ?;072V 70 @0EC=>: ?@83=VG5==O CYP3A4. 4=>G0A=5 70AB>AC20==O F8E ;V:0@AL:8E 70A>1V2 ?>B5=FV9=> <>65 ?@872>48B8 4> ?V428I5==O @878:C @>728B:C :0@4V>B>:A8G=>ABV (?>4>265==O V=B5@20;C QT, ?0@>:A87<0;L=0 H;C=>G:>20 B0EV:0@4VO B8?C «?V@C5B») B0, O: =0A;V4>:, 4> @0?B>2>W A5@F52>W A<5@BV. !;V4 C=8:0B8 70AB>AC20==O :><1V=0FVW 40=8E ;V:0@AL:8E 70A>1V2. !CAC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2 28<030T >15@56=>ABV B0 :>@83C20==O 4>78.
?;82 V=H8E ;V:0@AL:8E 70A>1V2 =0 D;C:>=07>;:
>A;V465==O 270T<>4VW ?@>45<=>AB@C20;8, I> >4=>G0A=5 26820==O W6V, F8<5B848=, 0=B0F848 01> ?>40;LH5 ?>@>3> BV;0 4;O ?5@5A04:8 :VAB:>2>3><>7:C =5 <0T ;V=VG=> 7=0GCI>3> ??;82C =0 01A>@1FVN D;C:>=07>;C ?@8 9>3> ?5@>@0;L=>AC20==V.
8D0 4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 @8D048;> 4> 7=865==O ?;>IV ?V4 :@82>N «:>=F5=B@0FVO-G0A» (AUC) =0 25 % B0 A:>@>GC20;> ?5@V>4 =0?V2282545==O D;C:>=07>;C =0 20 %. ">A>2CNBL @8D073;O=CB8 4>FV;L=VABL ?V428I5==O 4>78 D;C:>=07>;C.
?;82 D;C:>=07>;C =0 V=HV ;V:0@AL:V 70A>18.
\$;C:>=07>; T ?>BC6=8< V=3V1VB>@>< V7>D5@<5=BC 2C9 F8B>E@>AC20==V V7 D;C:>=07>;< VA=CT @878: ?V428I5==O C ?;072V :>=F5=B@0FV9 V=H8E A?>;C,; I> <5B01>;V7CNBLAO CYP2C9, CYP2C19 B0 CYP3A4. ">A>2C20B8 B0:V :><1V=0FVW ?@5?0@0BV2 A;V4 7 >15@56=VABN; ?@8 FL> 1EV4=> @5B5;L=> A?>AB5@V30B8 70 AB0=< ?0FVT=BV2. @83=VGC20;L=0 4VO D;C:>=07>;C =0 D5@<5=B8 715@V30TBLAO ?@>B03< 4-5 4V1 ?VA;O 9>3> 70AB>AC20==O C 7207:C 7 9>3> B@820;8 < ?5@V>4< =0?V2282545==O.
;LD5=B0=V;. V4 G0A >4=>G0A=>3> 70AB>AC20==O 0;LD5=B0=V;C C 4>7V 20=07>;C C 4>7V 400 <3 74>@>28< 4>1@>2>;LFO< A?>AB5@V30;>AO 42>:@0B=5 71V;LH5==O AUC₁₀, <>6;82>; G5@57 V=3V1C20==O CYP3A4. >65 1CB8 =5>1EV4=8< :>@83C20==O 4>78 0;LD5=B0=V;C.
, =>@B@8?B8;V=. \$;C:>=07>; ?>A8;NT 4VN 0@B@8?B8;V=C. 5:><5=4CTBLAO 28=F5=B@0FVW 5->=>@B@8?B8;V=C B0/01> S-0G0B:C :><1V=>20=>W B5@0?VW B0 G5@57 1 B8645=L. # @07V =5>1EV4=>ABV A;V4 2V4:>@83C20B8 4>7C 0@B@8?B8;V=C.
B5@8F8= . 4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 0B5@8F8=C V=DV:>20=8< <8H0< V7 =>@ <0;L=8< V< B0 V=DV:>20=8< <8H0< 7V 7=865=8< V< ?@8725;> 4> B0:8E @57C;LB0BV2: =525;8:89 048B82=89 ?@>B83@81:>289 5D5:B ?@8 A8AB5<=V9 V=D5:FVW
C. albicans, 2V4ACB=VABL 270T<>4VW ?@8 2=CB@VH=L>G5@5?=V9 V=D5:FVW *Cryptococcus neoformans* B0 0=B03>=V7< 42>E ?@5?0@0BV2 ?@8 A8AB5<=V9 V=D5:FVW *Aspergillus fumigatus*. ;V=VG=5 7=0G5==O @57C;LB0BV2, >B@8<0=8E C E>4V F8E 4>A;V465=L, =52V4<5. =B8:>03C;O=B8. !: V ?@8 70AB>AC20==V V=H8E 07>;L=8E ?@>B83@81:>28E 70A>1V2, ?@8 >4=>G0A=>AC20==V D;C:>=07>;C B0 20@D0@8=C ?>2V4<<O;>AO ?@> 28?04:8 @>728B:C :@>2>B5G (35<0B<<, =>A>2>W :@>2>B5GV, H;C=:>2>:8H:>28E :@>2>B5G, 35<0BC@VW B0 <5;5=8) C ?>T4=0==V 7 ?>4>265==O< ?@>B@><1V=>2>3> G0AC. @8 >4=>G0A=>AC20==V D;C:>=07>;C B0 20@D0@8=C A?>AB5@V30;>AO 42>:@0B=5 ?V428I5==O ?@>B@><1V=>2>3> G0AC, V<>2V@=>, 2=0A;V4>: ?@83=VG5==O <5B01>;V7 :>=B@>;N20B8 ?@>B@><1V=>289 G0A C ?0FVT=BV2, O:V >4=>G0A=> 70AB>A>2CNBL :C<0@8=>2V 0=B8:>03C;O=B8. >65 1CB8 =5>1EV4=>N :>@5:FVO 4>78 20@D0@8=C.
5=7>4V075?V=8 :>@>B:>W 4VW, =0?@8:;04;0<, B@807>;0 @87=0G5==O D;C:>=07>;C ?VA;O ?5@>@0;L=>3> 70AB>AC20==O ;048;> 4> 7=0G=>3> ?V428I5==O :>=F5=B@0FVW ;0 ?>A8;5==O ?A8E> <>B>@=8E 5D5:BV2. 4=>G0A=5 70AB>AC20==O D;C:>=07>;C C 4>7V 200 <3 B0 ;07V 7,5 <3 ?5@>@0;L=> ?@872>48;> 4> ?V428I5==O AUC B0 ?5@V>4C =0?V2282545==O C 3,7 B0 2,2 @070 2V4?>2V4=>. 0AB>AC20==O D;C:>=07>;C C 4>7V 200 <3/4>1C B0 0,25 <3 B@807>;0@0;L=> ?@872>48;> 4> ?V428I5==O AUC B0 ?5@V>4C =0?V2282545==O C 4,4 B0 2,3 @070 2V4?>2V4=>. @8 >4=>G0A=>AC20==V D;C:>=07>;C B0 B@807>;0AB5@V30;>AO ?>B5=FVN20==O B0 ?@>;>=30FVO 5D5:BV2 B@807>;>0

/:I> ?0FVT=BC, O:89 ?@>E>48BL :C@A ;V:C20==O D;C:>=07>;<, A;V4 >4=>G0A=> ?@87=0G8B8 B5@0?VN 15=7>4V075?V=0<8, 4>7C >AB0==VE A;V4 7<5=H8B8 B0 2AB0=>28B8 =0;56=89 =03;O4 70 AB0=>< ?0FVT=B0.

0@10<075?V=. \$.>C:>=07>; ?@83=VGCT <5B01>;V7< :0@10<075?V=C B0 A?@8G8=OT ?V428I5==O @V2=O :0@10<075?V=C 2 A8@>20BFV :@>2V =0 30 %. A=CT @878: @>728B:C ?@>O2V2 B>:A8G=>ABV 7 1>:C :0@10<075?V=C. >65 1CB8 =5>1EV4=8< :>@83C20==O 4>78 :0@10<075?V=C 70;56=> 2V4 @V2=O 9>3> :>=F5=B@0FVW B0 4VW ?@5?0@0BC.

;:>:0B>@8 :0;LFFVT28E :0=0;V2. 5O:V 0=B03>=VAB8 :0;LFFVN (=VD548?V=, VA@048?V=, 0<;>48?V= B0 D5;>48?V=) <5B01>;V7CNBLAO D5@<5=B>< CYP3A4. \$.>C:>=07>; ?>B5=V9=> <>65 ?V428IC20B8 A8AB5<=C 5:A?>78FVN 1;>:0B>@V2 :0;LFFVT28E :0=0;V2. 5:><5=4>20=89 @5B5;L=89 <=>VB>@8=3 I>4> @>728B:C ?>1VG=8E @50:FV9.

?5:>:A8I. @8 >4=>G0A=>AC20==V D;C:>=07>;C (200 <3 =0 4>1C) B0 F5;5:>:A81C (200 <3) <0:A8 <0;L=0 :>=F5=B@0FVO (C_{max}) B0 AUC F5;5:>:A81C ?V428IC20;8AO =0 68 % B0 134 % 2V4?>2V4=>. @8 >4=>G0A=>AC20==V F5;5:>:A81C B0 D;C:>=07>;C <>65 1CB8 =5>1EV4=8< 7<5=H5==O 4>78 F5;5:>:A81C 242VGV.

?>D>AD0 4=>G0A=5 70AB>AC20==O F8;>D>AD0=07>;C ?@872>48BL 4> ?V428I5==O @V2=O 1V;V@C1V=C B0 :@50B8=V=C 2 A8@>20BFV :@>2V. &V ?@5?0@0B8<>6=0 70AB>A>2C20B8 >4=>G0A=>, 72060NG8 =0 @878: ?V428I5==O :>=F5=B@0FVW 1V;V@C1V=C B0 :@50B8=V=C 2 A8@>20BFV :@>2V.

\$5=B0=V;.>2V4><;O;>AO ?@> >48= ;5B0;L=89 28?04>: V=B>:A8:0FVW D5=B0=V;< 2=0A;V4>: <>6;82>W 270T<>4VW D5=B0=V;C B0 D;C:>=07>;C. > B>3> 6, C 4>A;V465==V 7 CG0ABN 1274>@>28E 4>1@>2>;LFFV2 1C;> ?@>45<>=AB@>20=>, I> D;C:>=07>; 7=0G=> C?>2V;L=N202 5;V=F5=B@0FVW D5=B0=V;C <>65 ?@8725AB8 4> ?@83=VG5==O 48E0==O, B> :>=B@>;N20B8 AB0= ?0FVT=B0. >65 1CB8 =5>1EV4=>N :>@5:FVO 4>78 D5=B0=V;C.

=3V1VB>@8 ->-@54C:B078. !CAC20==O D;C:>=07>;C B0 V=3V1VB>@V2 -oA-@54C:B078, I> <5B01>;V7CNBLAO CYP3A4 (0B>@20AB0B8= B0 A8<20AB0B8=), 01> V=3V1VB>@V2 -oA-@54C:B078, I> <5B01>;V7CNBLAO CYP2C9 (D;C20AB0B8=), ?V428ICT @878: @>728B:C ?0BVW B0 @014>;V7C. # @07V =5>1EV4=>ABV >4=>G0A=>3> 70AB>AC20==O F8E ?@5?0@0BV2 A;V4 @5B5;L=> A?>AB5@V30B8 70 ?0FVT=B< I>4> 28=8:=5==O A8?0BVW B0 @014>;V7C V ?@>2>48B8 <=>VB>@8=3 @V2=O :@50B8=:V=078. # 28?04:C 7=0G=>3> ?V428I5==O @V2=O :@50B8=:V078, 0 B0:>6 ?@8 4V03=>ABC20==V 01> ?V4>7@V =0 ?0BVN/@014>;V7 70AB>AC20==O V=3V1VB>@V2 -oA-@54C:B078 A;V4 ?@8?8=8B8.

AC?@5A>@8 (=0?@8;:04 F8;:>A?>@8=, 525@>;V;V;V ?>A?>@8=. \$.>C:>=07>; 7=0G=> ?V428ICT :>=F5=B@0FVN B0 AUC F8;>A?>@8=C. @8 >4=>G0A=> AC20==V D;C:>=07>;C C 4>7V 200 <3/4>1C B0 F8;>A?>@8=C C 4>7V 2,7 <3/:3/4>1C A?>AB5@V30;>AO 71V;LH5==O AUC F8;>A?>@8=C C 1,8 @070. &V ?@5?0@0B8 <>6=0 70AB>A>2C20B8 >4=>G0A=> 70 C <>28 7<5=H5==O 4>78 F8;>A?>@8=C 70;56=> 2V4 9>3> :>=F5=B@0FVW.

25@>;V %>G0 4>A;V465=L in vitro B0 in vivo =5 ?@>2>48;8, D;C:>=07>; <>65 ?V428IC20B8 :>=F5=B@0FVN 525@>;V20BFV :@>2V G5@57 ?@83=VG5==O CYP34.

!8@>;V \$.>C:>=07>; ?V428ICT :>=F5=B@0FVN A8@>;V2V, V<>2V@=>, H;OE<< ?@83=VG5==O <5B01>;V7;V 2V4 @V2=O :>=F5=B@0FVW B0 5D5:BV2 ?@5?0@0BC.

"0:@>;V \$.>C:>=07>; <>65 ?V428IC20B8 :>=F5=B@0FVW B0:@>;V20BFV :@>2V 4> 5 @07V2 ?@8 9>3> ?5@>@0;L=>AC20==V G5@57 ?@83=VG5==O <5B01>;V7;VAC20==V B0:@>;VAB5@V30;>AO 7=0G=8E 7FVNNBLAO V7 =5D@>B>:A8G=VABN. >7C B0:@>;V@0;L=>3> 70AB>AC20==O A;V4 7 <5=H8B8 70;56=> 2V4 :>=F5=B@0FVW B0:@>;V

>70@B0=. \$.>C:>=07>; ?@83=VGCT <5B01>;V7< ;>70@B0=C 4> 9>3> 0:B82=>3> <5B01>;VBC (E-3174), I> 7C<>2;NT 1V;LHC G0AB8=C 0=B03>=V7 @5F5?B>@V2 0=3V>B5=78=C II ?V4 G0A 70AB>AC20==O ;>70@B0=C. 5:><5=4>20=> 74V9A=N20B8 ?>ABV9=89 <=>VB>@8=3 0@B5@V0;L=>3> B8A:C C ?0FVT=BV2.

5B04>=. \$.>C:>=07>; <>65 ?V428IC20B8 :>=F5=B@0FVN <5B04>=C C A8@>20BFV :@>2V. @8 >4=>G0A=>AC20==V <5B04>=C B0 D;C:>=07>;C <>65 1CB8 =5>1EV4=8< :>@83C20==O 4>78 <5B04>=C.

5AB5@>W4=V ?@>B870?0;L=V ?@5?0@0B8 (). @8 >4=>G0A=>AC20==V 7 D;C:>=07>;< C_{max} B0 AUC D;C@1V?@>D5=C ?V428IC20;8AO =0 23 % B0 81 % 2V4?>2V4=> ?>@V2=O=> 7 2V4?>2V4=8<8 ?>:07=8:0<8 ?@8 70AB>AC20==V BV;L:8 D;C@1V?@>D5=C. =0;>3VG=> ?@8 >4=>G0A=>

70AB>AC20==V D;C:>=07>;C 7 @0F5_{max} B0 AUC D0@<0>;>3VG=> 0:B82=>3> V7><5@C S-(+)-
V1C?@>D5=C ?V428IC20;8AO =0 15 % B0 82 % 2V4?>2V4=> ?>@V2=O=> 7 B0:8<8 ?>:07=8:0<8 ?@8
70AB>AC20==V BV;L:8 @0F53> V1C?@>D5=C.
%>G0 A?5FV0;L=8E 4>A;V465=L =5 ?@>2>48;8, D;C:>=07>; ?>B5=FV9=> 740B=89 ?V428IC20B8 A8AB5
<=C 5:A?>78FVN V=H8E , I> <5B01>;V7CNBLAO CYP2C9 (=0?@8:;04 =0?@>:A5=C, ;>@=>:A8:0
D5=0:C). 5:><5=4>20=> ?5@V>48G=> 74V9A=N20B8 <=>VB>@8=3 ?>1VG=8E @50:FV9 B0 B>:A8G=8E
?@>O2V2, ?>2O70=8E V7 . >65 7=04>18B8AO :>@83C20==O 4>78 .
\$5=VB>W=. \$;C:>=07>; ?@83=VGCT <5B01>;V7< D5=VB>W=C 2 ?5GV=FV. 4=>G0A=5 1030B>@07>25
70AB>AC20==O 200 <3 D;C:>=07>;C B0 250 <3 D5=VB>W=C 2=CB@VH=L>25==> ?@872>48BL 4>
?V428I5==O AUC₂₄ D5=VB>W=C =0 75 % B0 !_{min}=0 128 % . @8 >4=>G0A=>AC20==V F8E ;V:0@AL:8E
70A>1V2 A;V4 ?@>2>48B8 <=>VB>@8=3 :>=F5=B@0FVW D5=VB>W=C C A8@>20BFV :@>2V 4;O
C=8:=5==O @>728B:C B>:A8G=>W 4VW D5=VB>W=C.
@54=V7>=. >2V4><;O;>AO ?@> 28?04>;, :>;8 C ?0FVT=B0 ?VA;O B@0=A?;0=B0FVW ?5GV=:8 =0 B;V
70AB>AC20==O ?@54=V7>=C @>728=C;0AO 3>AB@0 =54>AB0B=VABL :>@8=04=8@>:28E 70;>7, I>
28=8:;0 ?VA;O ?@8?8=5==O B@83> :C@AC B5@0?VW D;C:>=07>;>AC20==O D;C:>=07>;C, V<>2V@=>,
A?@8G8=8;> ?>A8;5==O 0:B82=>ABV CYP3A4, I> ?@8725;> 4> ?@8H284H5==O <5B01>;V7=C. !;V4
@5B5;L=> AB568B8 70 ?0FVT=B0<8, O:V ?@>B03< B@820;>3> G0AC >4=>G0A=> 70AB>A>2CNBL
D;C:>=07>; B0 ?@54=V7>=. 7 <5B>N ?>?5@5465==O @>728B:C =54>AB0B=>ABV :>@8 =04=8@>:28E
70;>7 ?VA;O ?@8?8=5==O 70AB>AC20==O D;C:>=07>;C.
8D01CB8=. \$;C:>=07>; ?V428ICT :>=F5=B@0FVN @8D01CB8=C 2 A8@>20BFV :@>2V, I> ?@872>48BL
4> 71V;LH5==O AU! @8D01CB8=C 4> 80 % . @8 >4=>G0A=>AC20==V D;C:>=07>;C B0 @8D01CB8=C
?>2V4><;O;>AO ?@> 28?04:8 @>728B:C C25WBC. @8 70AB>AC20==V B0:>W :><1V=0FVW
;V:0@AL:8E 70A>1V2 A;V4 1@0B8 4> C2038 A8<8 B>:A8G=>W 4VW @8D01CB8=C.
!0:2V=02V@. \$;C:>=07>; ?V428ICT AUC B0 C_{max} A0:2V=02V@C ?@81;87=> =0 50 % B0 55 %
2V4?>2V4=> G5@57 ?@83=VG5==O <5B01>;V7 P-3;V:>?@>B5W=C. 70T<>4VW =07>;> B0
A0:2V=02V@=>02V@< =5 4>A;V46C20;8AO, B>=8 <>6CBL 1CB8 1V;LH 28@065=8<8. >65 1CB8
=5>1EV4=8< :>@83C20==O 4>78 A0:2V=02V@C.
>EV4=V AC;LD>=V;A5G>28=8. @8 >4=>G0A=>AC20==V D;C:>=07>; ?@>;>=3CT ?5@V>4
=0?V2282545==O ?5@>@0;L=8E ?>EV4=8E AC;LD>=V;A5G>28=8 (E;>@?@>?0;1CB0AC20==V 74>@>28
< 4>1@>2>;LFO<5=4CTBLAO ?@>2>48B8 G0AB89 :>=B@>;L FC:@C 2 :@>2V B0 2V4?>2V4=8< G8=><
7=86C20B8 4>7C ?>EV4=8E AC;LD>=V;A5G>28=8 ?@8 >4=>G0A=>AC20==V V7 D;C:>=07>;>
"5>DV;V=. # 4>A;V465==V 270T<>4VW ?@5?0@0BV2 70AB>AC20==O D;C:>=07>;C ?> 200 <3
?@>B03<< 14 4=V2 ?@8725;> 4> 7=865==O A5@54=L>3> ;V@5=AC B5>DV;V=C 2 ?;072V =0 18 % . 0
?0FVT=B0<8, O:V 70AB>A>2CNBL B5>DV;V= C 28A>:8E 4>70E 01> O:V<0NBL ?V428I5=89 @878:
@>728B:C B>:A8G=8E ?@>O2V2 B5>DV;V=C 7 V=H8E ?@8G8=, A;V4 2AB0=>28B8 =03;04 I>4>
28O2;5==O >7=0: @>728B:C B>:A8G=>W 4VW B5>DV;V=C. "5@0?VN A;V4 7O2V >7=0: B>:A8G=>ABV.
;:0;>W48 10@2V=:C. %>G0 2V4?>2V4=8E 4>A;V465=L =5 ?@>2>48;8, D;C:>=07>;, V<>2V@=>, G5@57
V=3V1C20==O CYP3A4, <>65 A?@8G8=OB8 ?V428I5==O :>=F5=B@0FVW 0;:0;>W4V2 10@2V=:C C ?;07
2V (=0?@8:;04 2V=:@8AB8=C B0 2V=1;0AB8=C), I> ?@872>48BL 4> @>728B:C =59@>B>:A8G=8E
5D5:BV2.
VB0 >2V4><;O;>AO, I> C ?0FVT=B0, O:89 >4=>G0A=> 70AB>A>2C202 B@0=A@5B8=>T2C :8A;>BC
(:8A;>B=0 D>@<0 2VB0=07>;, A?>AB5@V30;8AO ?>1VG=V @50:FVW 7 1>:C &! C D>@BC<>@C
3>;>2=>3> <>7:C; 40=89 5D5:B 7=8: ?VA;O 2V4=07>;C. &V ;V:0@AL:V 70A>18<>6=0 70AB>A>2C20B8
>4=>G0A=>, 0;5 A;V4 ?0<OB0B8 ?@> @878: 28=8:=5==O ?>1VG=8E @50:FV9 7 1>:C &!.
>@8:>=07>; (V=3V1VB>@ CYP2!9, CYP2!19 B0 CYP34). 4=>G0A=5 70AB>AC20==O 2>@8:>=07>;C
?5@>@0;L=> (?> 400 <3 :>6=V 12 3>48= ?@>B03<< 1 4=O, ?>BV< ?> 200 <3 :>6=V 12 3>48= ?@>B03<<
2,5 4=O) B0 D;C:>=07>;C ?5@>@0;L=> (400 <3 C ?5@H89 45=L, ?>BV< ?> 200 <3 :>6=V 24 3>48=8
?@>B03<< 4 4=V2) 8 74>@>28< 4>1@>2>;LFO< G>;>2VG>W AB0BV ?@8725;> 4> ?V428I5==O !_{max} B0
AUC 2>@8:>=07>;C 2 A5@54=L> 57 % (90 % : 20 %, 107 %) B0 79 % (90 % : 40 %, 128 %) 2V4?>2V4=>.
52V4><>, G8 ?@872>48BL 7=865==O 4>78 B0/01> G0AB>B8 70AB>AC20==O 2>@8:>=07>;C 01>
D;C:>=07>;C 4> CAC=5==O B0:>3> 5D5:BC. @8 70AB>AC20==V 2>@8:>=07>;C ?VA;O D;C:>=07>;C
A;V4 ?@>2>48B8 A?>AB5@565==O I>4> @>728B:C ?>1VG=8E 5D5:BV2, 0A>FV9>20=8E V7
2>@8:>=07>;>
84>2C48=. \$;C:>=07>; ?V428ICT !_{max} B0 AUC 784>2C48=C =0 84 % B0 74 % 2V4?>2V4=>, I> 7C<>2;5=>
7=865==O< ;V@5=AC 784>2C48=C ?@81;87=> =0 45 % ?@8 9>3> ?5@>@0;L=>AC20==V. 5@V>4

=0?V2282545==O 784>2C48=C 1C2 B0:>6 ?>4>265=89 ?@81;87=> =0 128 % ?VA;O 70AB>AC20==O :>
<1V=0FVW D;C:>=07>;C B0 784>2C48=C. 0 ?0FVT=B0<8, O:V 70AB>A>2CNBL B0:C :<1V=0FVN
;V:0@AL:8E 70A>1V2, A;V4 A?>AB5@V30B8 I>4> @>728B:C ?>1VG=8E @50:FV9, ?>2O70=8E V7
70AB>AC20==O< 784>2C48=C. >6=0 @>73;O=CB8 4>FV;L=VABL 7=865==O 4>78 784>2C48=C.
78B@> # E>4V 2V4:@8B>3> @0=4>20=>3> B@L>EAB>@>==L>3> ?5@5E@5A=>3> 4>A;V465==O
>FV=N20;8 2?;82 078B@>=07>;C =0 D0@<0:>:V=5B8:C >48=>4=>3> ?@8 WE >4=>G0A=>@0;L=>2>
AC20==V C 4>70E 1200 <3 B0 800 <3 2V4?>2V4=>. >4=8E 7=0GCI8E D0@<0:>:V=5B8G=8E 270T<>4V9
28O2;5=> =5 1C;>.

5@>@0;L=V :>=B@0F5?B828. @>2>48;8AO 4>A;V465==O 1030B>@07>2>3> 70AB>AC20==O
D;C:>=07>;C B0 :<1V=>20=>3> ?5@>@0;L=>3> :>=B@0F5?B820. @8 70AB>AC20==V D;C:>=07>;C C
4>7V 50 <3 2?;82C =0 @V25=L 3>@<=>V2 =5 1C;>; B>4V O: ?@8 70AB>AC20==V D;C:>=07>;C C 4>7V
200 <3 =0 4>1C A?>AB5@V30;>AO 71V;LH5==O U! 5B8=V;5AB@04V>;C =0 40 % B0
;52>=>@35AB@5;C =0 24 %. &5 A2V4G8BL ?@> B5, I> 1030B>@07>25 70AB>AC20==O D;C:>=07>;C C
707=0G5=8E 4>70E =02@O4 G8 <>65 2?;820B8 =0 5D5:B82=VABL :<1V=>20=>3> ?5@>@0;L=>3>
:>=B@0F5?B820.

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

5@<0B>DVBVVO. V4?>2V4=> 4> @57C;LB0BV2 4>A;V465==O D;C:>=07>;C 4;O ;V:C20==O 45@
<0B>DVBVW C 4VB59, D;C:>=07>; =5 ?5@528ICT 3@875>DC;L2V= 70 5D5:B82=VABN V 7030;L=89
?>.07=8: 5D5:B82=>ABV AB0=>28BL <5=H5 20 %. ">;® =5 A;V4 70AB>A>2C20B8 4;O ;V:C20==O 45@
<0B>DVBVW.

@8?B>:>:>7. >:07V2 5D5:B82=>ABV D;C:>=07>;C 4;O ;V:C20==O :@8?B>:>:>7C V=H8E
;>:0;V70FV9 (=0?@8;:04 ;535=52>3> :@8?B>:>:>7C B0 :@8?B>:>:>7C H:V@8) =54>AB0B=L>, B>
<5=40FV9 I>4> 4>7>2>3> @568@N20=L =5<0T.

;81>:V 5=4578. >:07V2 5D5:B82=>ABV D;C:>=07>;C 4;O ;V:C20==O V=H8E D>@ 5=457V2, B0:8E
O: ?0@0:>:F84i>W4>7, 3VAB>?;07<>7 B0 H:V@=>-;V@>B@8E>7, =54>AB0B=L>, B><5=40FV9 I>4>
4>7>2>3> @568@N20=L =5<0T.

8@:>20 A8AB5<0. 0FVT=B0< V7 ?>@CH5==O< DC=:FV9 =8@>: ?@5?0@0B A;V4 70AB>A>2C20B8
7 >15@56=VABN.

5?0B>1V;V0@=0 A8AB5<0. 0FVT=B0< V7 ?>@CH5==O< DC=:FV9 ?5GV=:8 ?@5?0@0B A;V4
70AB>A>2C20B8 7 >15@56=VABN. 0AB>AC20==O D;C:>=07>;C 0A>FVN20;>AO 7 28=8:=5==O<
@V4:VA=8E 28?04:V2 @>728B:C BO6:>W 35?0B>B>:A8G=>ABV, 2;:;NG0NG8 ;5B0;L=V 28?04:8,
3>;>2=8< G8=< C ?0FVT=V2 V7 BO6:8<8 >A=>2=8<8 70E2>@N20==O<8. # 28?04:0E, :>8
@>728B>: 35?0B>B>:A8G=>ABV 0A>FVN202AO V7 70AB>AC20==O< D;C:>=07>;C, =5 1C;>
2V47=0G5=> WW O2=>W 70;56=>ABV 2V4 7030;L=>W 4>1>2>W 4>78 ?@5?0@0BC, B@820;>ABV
B5@0?VW, AB0BV 01> 2V:C ?0FVT=B0. 0728G09 35?0B>B>:A8G=VABL, A?@8G8=5=0 D;C:>=07>;>
<, >1>@>B=0, 0 WW ?@>O28 7=8:0NBL ?VA;O ?@8?8=5==O B5@0?VW.

0 ?0FVT=B0<8, C O:8E ?@8 70AB>AC20==V D;C:>=07>;C A?>AB5@V30NBLO 2V4E8;5==O
@57C;LB0BV2 DC=:FV=>0;L=8E ?@>1 ?5GV=:8, A;V4 2AB0=>28B8 @5B5;L=89 =03;O4 I>4>
@>728B:C 1V;LH BO6:>3> C@065==O ?5GV=:8.

0FVT=V2 A;V4 ?@>V=D>@A8<8, I> <>6CBL A2V4G8B8 ?@> A5@9>7=89 2?;82 =0 ?5GV=:C
(28@065=0 0AB5=VO, 0=>@5:AVO, ?>ABV9=0 =C4>B0, 1;N20==O B0 6>2BO=8FO). # B0:>
AC20==O D;C:>=07>;C A;V4 =5309=> ?@8?8=8B8 B0 ?@>:=AC;LBC20B8AO 7 ;V:0@5

!5@F52>-AC48==0 A8AB5<0. 5O:V 07>;8, C B>=07>;, 0A>FVNNBLAO V7 ?>4>265==O<
V=B5@20;C Q" =0 5;5:B@>:0@4V>3@QV4><;O;>AO ?@> 4C65 @V4:VA=V 28?04:8 ?>4>265==O
V=B5@20;C Q" B0 ?0@>:A87<0;L=>W H;C=>G:>2>W B0EV:0@4VW B8?C «?V@C5B» ?@8
70AB>AC20==V ?@5?0@0BC \$;C=>;®. "0:V ?>2V4><;5==O AB>AC20;8AO ?0FVT=V2 V7 BO6:8<8
70E2>@N20==O<8 ?@8 ?>T4=0==V 1030BL>E D0:B>@V2 @878:C, B0:8<8 O: AB@C:BC@=V
70E2>@N20==O A5@FO, ?>@CH5==O 5;5:B@>;VB=>3> >#=>G0A=5 70AB>AC20==O V=H8E
;V:0@AL:8E 70A>1V2, I> 2?;820NBL =0 V=B5@20; Q".

\$;C=>;® A;V4 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< V7 @878:< @>728B:C 0@8BG0A=5
70AB>AC20==O @07<< V7 ;V:0@AL:8<8 70A>10<8, I> ?@>;>=3CNBL V=B5@20; QTA B0
<5B01>;V7CNBLAO 70 4>?><>3>N D5@<5=BC CYP34 F8B>E@>B8?>:070=5.

0;>D0=B@8=. 0;>D0=B@8= T AC1AB@0B< D5@<5=BC CYP34 V ?@>;>=3CT V=B5@20; QTA ?@8
70AB>AC20==V C @5:><5=4>20=8E B5@0?52B8G=8E 4>70E. 4=>G0A=5 70AB>AC20==O
30;>D0=B@8=C B0 D;C:>=07>;C =5 @5:><5=4CTBLAO.

5@<0B>;>3VG=V @50:FVW. V4 G0A 70AB>AC20==O D;C:>=07>;C @V4:> ?>2V4<;O;>AO ?@>
@>728B>: B0:8E 5:AD>;V0B82=8E H:V@=8E @50:FV9 O: A8=4@< !BV25=A0-6>=A>=0 B0
B>:A8G=89 5?V45@<0;L=89 =5:@>;V7. 0FVT=B8 7V !< 1V;LH AE8;L=V 4> @>728B:C B06:8E
H:V@=8E @50:FV9 ?@8 70AB>AC20==V 1030BL>E ;V:0@AL:8E 70A>1V2. /!> C ?0FVT=B0 V7
?>25@E=52>N 3@81:>2>N V=D5:FVTN 7O2;ONBLAO 28A8?0==O, I><>6=0 ?>2O70B8 V7
70AB>AC20==O< D;C:>=07>;C, ?>40;LH5 70AB>AC20==O ?@5?0@0BC A;V4 ?@8?8=8B8. /!> C
?0FVT=B0 7 V=20782=>N/A8AB5<=>N 3@81:>2>N V=D5:FVTN 7O2;ONBLAO 28A8?0==O =0
H:V@V, 70 9>3> AB0=< ?>B@V1=> @5B5;L=> A?>AB5@V30B8, 0 C 28?04:C @>728B:C
1C;L>7=8E 28A8?0=L 01> @<=>W 5@8B5<8 70AB>AC20==O D;C:>=07>;C A;V4 ?@8?8=8B8.
V?5@GCB;82VABL. # @V4:VA=8E 28?04:0E ?>2V4<;O;>AO ?@> @>728B>: 0=0DV;0:B8G=8E @50:FV9.
&8B>E@>< 450. \$;C:>=07>; T ?>BC6=8< V=3V1VB>@<< D5@<5=BC CYP2C9 B0 ?>® B0 ?@5?0@0B8 7
2C7L:8< B5@0?52B8G=8< 2V:=<, I> <5B01>;V7CNBLAO 7 CG0ABN CYP2C9, CYP2C19 B0 CYP3A4.
"5@D5=048=. !;V4 @5B5;L=> A?>AB5@V30B8 70 AB0=< ?0FVT=B0 ?@8 >4=>G0A=>AC20==V
B5@D5=048=C B0 D;C:>=07>;C C 4>7V <5=H5 400 <3 =0 4>1C.
>?>28=8. @5?0@0B 7C. 0FVT=B0< 7 @V4:VA=8<8 A?04:>28<8 70E2>@N20==O<8, B0:8<8 O:
=5?5@5=>A878, =54>AB0B=VABL ;0:B078 0?0 B0<0;L01A>@1FVO 3;N:>78-30;0:B>78, =5 A;V4
70AB>A>2C20B8 F59 ?@5?0@0B.

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

0=V, >B@8<0=V ?@8 @07>2> ?>2B>@=>AC20==V D;C:>=07>;C C 728G09=8E 4>70E
(< 200 <3/4>1C) 203VB=8< ?@>B03<< I B@8<5AB@C 203VB=>ABV, =5 ?@>45<>=AB@C20;8
=51060=8E 5D5:BV2 =0 ?;V4. >2V4<<;O;>AO ?@> G8A5;L=V 2@>465=V ?0B>;>3VW C
=>2>=0@>465=8E (2::NG0NG8 1@048D@5=VN, 48A?;07VN 2CH=>W @0:>28=8, =043> BV<OG:0,
28:@82;5==O AB53=0, ?;5G>;V:BL>289 A8=>AB>7), <0B5@V O:8E ?@89<0;8 28A>:V 4>78 D;C:>=07>;C
(400-800 <3/4>1C) ?@>B03<< ?@8=09<=V 3-E 01> 1V;LH5 :F84i>W4>7C. 2O7>: AC20==O< D;C:>=07>;C
B0 F8<8 28?04:0<8 =5 287=0G5=89.
5 A;V4 70AB>A>2C20B8 728G09=V 4>78 D;C:>=07>;C B0 :>@>B>B@820;V :C@A8 ;V:C20==O
D;C:>=07>;<< C ?5@V>4 203VB=>ABV, 70 28=OB:< :@09=L>W =5>1EV4=>ABV.
5 A;V4 70AB>A>2C20B8 28A>:V 4>78 D;C:>=07>;C B0/01> B@820;V :C@A8 ;V:C20==O D;C:>=07>;<< C
?5@V>4 203VB=>ABV, 70 28=OB:< ;V:C20==O V=D5:FV9, I> ?>B5=FV9=> 703@>6CNBL 68BBN.
\$;C:>=07>; ?@>=8:0T C 3@C4=5 <>;> B0 4>AO30T =86G>W :>=F5=B@0FVW =V6 C ?;072V. >4C20==O
3@C44N <>6=0 ?@>4>26C20B8 ?VA;O @07>2>3> 70AB>AC20==O 728G09=>W 4>78 D;C:>=07>;C, I>
AB0=>28BL 200 <3 01> <5=H5.
>4C20B8 3@C44N =5 @5:><5=4CTBLAO ?@8 1030B>@07>2>AC20==V D;C:>=07>;C 01> ?@8
70AB>AC20==V 28A>:8E 4>7 D;C:>=07>;C.

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.

>A;V465=L ??;82C ?@5?0@0BC \$;C=>;® =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01>
?@0FN20B8 7 V=H8<8 <5E0=V7<0<8 =5 ?@>2>48;8.
0FVT=BV2 A;V4 ?@>V=D>@ <>6;82VABL @>728B:C 70?0<>@>G5==O 01> AC4< ?V4 G0A
70AB>A>2C20==O ?@5?0@0BC \$;C=>;®. @8 @>728B:C B0:8E A8<5=4CTBLAO :5@C20B8
02B>B@0=A?>@B< 01> ?@0FN20B8 7 V=H8<8 <5E0=V7<0<8.

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

>1>20 4>70 D;C:>=07>;C 70;568BL 2V4 284C B0 B06:>ABV 3@81:>2>W V=D5:FVW. ;O 1V;LH>ABV
28?04:V2 203V=0;L=>3> :0=484>7C 4>AB0B=L> @07>2>3> 70AB>AC20==O ?@5?0@0BC.
@8 =5>1EV4=>ABV 1030B>@07>2>3> 70AB>AC20==O ?@5?0@0BC ;V:C20==O V=D5:FV9 A;V4
?@>4>26C20B8 4> 7=8:=5==O ;V=VG=8E B0 ;01>@0B>@=8E ?@>O2V2 0:B82=>ABV 3@81:>2>W
V=D5:FVW. 54>AB0B=O B@820;VABL ;V:C20==O<>65 ?@8725AB8 4> 2V4=>2;5==O 0:B82=>3>
V=D5:FV9=>3> ?@>F5AC.

@5?0@0B 70AB>A>2C20B8 ?5@>@0;L=>. !?>AV1 70AB>AC20==O ?@5?0@0BC 70;568BL 2V4
::V=VG=>3> AB0=C ?0FVT=B0. 5<0T =5>1EV4=>ABV C 71>2>W 4>78 ?@5?0@0BC ?@8 73>
70AB>AC20==O 7 ?5@>@0;L=>3> =0 2=CB@VH=L>25==89 B0 =02?0:8.
0?AC;8 A;V4 :>2B0B8 FV;8<8. @89>< ?@5?0@0BC =5 70;568BL 2V4 ?@89>
>@>A;V.
@8?B>:>:>7.
V:C20==O :@8?B>:>:>2>3><5=V=3VBC: =020=B06C20;L=0 4>70 AB0=>28BL 400<3 C ?5@H89 45=L.
V4B@870 200-400 <3/4>1C. "@820;VABL ;V:C20==O 70728G09 AB0=>28BL I>=09*5=H5 6-8 B86=V2.
@8 V=D5:FVOE, I> 703@>6CNBL 68BBN, 4>1>2C 4>7C <>6=0 71V;LH8B8 4> 800<3.
V4B@8?5@5465==O @5F8482C :@8?B>:>:>2>3><5=V=3VBC C ?0FVT=BV2 7 28A>:8< @878:>< 9>3>
@>728B:C: @5:><5=4>20=0 4>70 ?@5?0@0BC AB0=>28BL 200<3/4>1C ?@>BO3>< =5>1<565=>3>
G0AC.
>:F84i>W4>7. 5:><5=4>20=0 4>70 AB0=>28BL 200-400 <3/4>1C. "@820;VABL ;V:C20==O AB0=>28BL
11-24 2H5 70;56=> 2V4 AB0=C ?0FVT=B0. ;O ;V:C20==O 45O:8E D>@< V=D5:FVW, 0 >A>1;82> 4;O
;V:C20==O <5=V=3VBC, <>65 1CB8 4>FV;L=8< 70AB>AC20==O 4>78 800 <3/4>1C.
=20782=V :0=484>78. 020=B06C20;L=0 4>70 AB0=>28BL 800<3 C ?5@H89 45=L. V4B@870 400 <3/
4>1C. □0728G09 @5:><5=4>20=0 B@820;VABL ;V:C20==O :0=4845 AB0=>28BL 2 B86=V ?VA;O
?5@H8E =530B82=8E @57C;LB0BV2 :C;LBC@8 :@>2V B0 7=8:=5==O >7=0: V A8
0=484>7 A;87>28E >I>;>=>:.
0=484>7 @>B>3;>B:8: =020=B06C20;L=0 4>70 AB0=>28BL 200-400<3 C ?5@H89 45=L, ?V4B@870 100-
200 <3/4>1C. "@820;VABL ;V:C20==O AB0=>28BL 7-21 45=L (4> 4>AO3=5==O @50;5 <>65 1CB8
71V;LH5=0 4;O ?0FVT=BV2 V7 BO6:8< V45DVF8B>
0=484>7 AB@02>E>4C: =020=B06C20;L=0 4>70 AB0=>28BL 200-400<3 C ?5@H89 45=L, ?V4B@870 100-
200 <3/4>1C. "@820;VABL ;V:C20==O AB0=>28BL14-30 4=V2 (4> 4>AO3=5==O @5 4;O ?0FVT=BV2 V7
BO6:8< V45DVF8B>
0=484C@VO: @5:><5=4>20=0 4>70 AB0=>28BL 200-400 <3/4>1C ?@>BO3>< 7-21 4=V2. ;O ?0FVT=BV2
V7 BO6:8< V45DVF8B>< B@820;VABL ;V:C20==O<>6=0 71V;LH8B8.
%@>=VG=89 0B@>DVG=89 :0=484>7: @5:><5=4>20=0 4>70 AB0=>28BL 50<3/4>1C ?@>BO3><
14 4=V2.
%@>=VG=89 :0=484>7 H:V@8 B0 A;87>28E >I>;>=>: @5:><5=4>20=0 4>70 AB0=>28BL
50-100 <3/4>1C. "@820;VABL ;V:C20==O AB0=>28BL 4 28 4=V2, 0;5 <>65 1CB8 71V;LH5=0 70;56=> 2V4
BO6:>ABV B0 284C V=D5:FVW 01> 7=865==O V
>?5@5465==O @5F8482C :0=484>7C A;87>28E >I>;>=>: C ?0FVT=BV2 7, O:V<0NBL 28A>:89 @878:
9>3> @>728B:C.
0=484>7 @>B>3;>B:8, :0=484>7 AB@02>E>4C: @5:><5=4>20=0 4>70 AB0=>28BL
100-200 <3/4>1C 01> 200 <3 3 @078 =0 B8645=L. "@820;VABL ;V:C20==O T =5>k565=>N 4;O
?0FVT=BV2 V7 ?@83=VG5=8< V
@>DV;0:B8:0 :0=484>7=8E V=D5:FV9 C ?0FVT=BV2 V7 B@820;>N =59B@>?5=VTN. 5:><5=4>20=0
4>70 AB0=>28BL 200-400 <3. V:C20==O A;V4 @>7?>G8=0B8 70 :V;L:0 4=V2 4> >GV:C20=>3>
@>728B:C =59B@>?5=VW B0 ?@>4>26C20B8 ?@>BO3>< 7 4=V2 ?VA;O ?V428I5==O :V;L:>ABV
=59B@>DV;V2 ?>=04 1000/<<3.
5=VB0;L=V :0=484>78.
>AB@89 203V=0;L=89 :0=484>7, :0=484>7=89 10;0=VB: @5:><5=4>20=0 4>70 AB0=>28BL 150<3
@07>2>.
V:C20==O B0 ?@>DV;0:B8:0 @5F8482CNG8E 203V=0;L=8E :0=484>7V2 (4 01> 1V;LH5 28?04:V2 =0
@V:): @5:><5=4>20=0 4>70 AB0=>28BL 150<3 1 @07 =0 3 4=V. AL>3> A;V4 70AB>AC20B8 3 4>78 (1
45=L, 4 45=L B0 7 45=L). VA;O FL>3> A;V4 70AB>A>2C20B8 ?V4B@87C 150 <3 1 @07 =0 B8645=L
?@>BO3>< 6

5@<0B>78.

V:>7 AB>?, 7 3;045=L:>W H:V@8, ?0E>289 45@<0B>7, :0=484>7=V V=D5:FVW H:V@8: @5:><5=4>20=0
4>70 AB0=>28BL 150<3 1 @07 =0 B8645=L, 01> 50 <3 1 @07 =0 4>1C. "@820;VABL ;V:C20==O
AB0=>28BL 2-4 B86=V. V:C20==O7C AB>? <>65 B@820B8 4> 6 B86=V2.

V7=>10@2=89 ;8H09: @5:><5=4>20=0 4>70 AB0=>28BL 300-400 <3 1 @07 =0 B8645=L ?@>BO3<<
1-3 B86=V2.

5@<0B>DVB=89 >=VE>7: @5:><5=4>20=0 4>70 AB0=>28BL 150 <3 1 @07 =0 B8645=L. V:C20==O A;V4
?@>4>26C20B8 ?>:8 =0 20=>3> =V3BO 28@>AB5 74>@>289. ;O 2V4@>AB0==O 74>@>28E =V3BV2 =0
@C:0E B0 =0 25;8:8E ?0;LFOE =V3 70728G09 =5>1EV4=>
3-6 2V4=>. 4=0: H284:VABL @>ABC =V3BV2 C ?0FVT=BV2 <>65 1CB8 @V7=>N B0 70;560B8 2V4 2V:C.
VA;O CA?VH=>3> ;V:C20==O B@820;8E E@>=VG=8E V=D5:FV9 D>@<0 =V3BO V=>4V 70;8H0TBLAO
7N.

VB8.

0AB>A>2C20B8 ;V:0@AL:89 70AV1 C D>@@VW ?0FVT=BV2 <>6=0 B>4V, :>;8 4VB8 740B=V 157?5G=>
?@>:>2B=CB8 :0?AC;C, I> 70728G09 T <>6;828< C 2VfV 2V4 5 @>:V2.

5 A;V4 ?5@528IC20B8 <0:A8<0;L=C 4>1>2C 4>7C 400 <3.

/: V ?@8 0=0;>3VG=8E V=D5:FVOE C 4>@>A;8E, B@820;VABL ;V:C20==O 70;568BL 2V4 ;V=VG=>W
B0 ;>3VG=>W 2V4?>2V4V. \$;C=>;® A;V4 70AB>A>2C20B8 1 @07 =0 4>1C.

>7C20==O ?@5?0@0BC 4VBO< V7 ?>@CH5==O< DC=:FV9 =8@>: =02545=> =86G5. \$0@<0>:V=5B8:0
D;C:>=07>;C =5 4>A;V46C20;0AO C 4VB59 V7 =8@>:>2>N =54>AB0B=VABN.

VB8 2V:>< 2V4 12 @>:V2.

0;56=> 2V4 <0A8 BV;0 B0 ?C15@B0B=>3> @>728B:C ;V:0@N A;V4 >FV=8B8, O:0 4>70 ?@5?0@0BC
(4;O 4>@>A;8E G8 4;O 4VB59) T >?B8<0;L=>N 4;O ?0FVT=B0. ;V=VG=V 40=V A2V4G0BL ?@> B5, I> C
4VB59 ;V@5=A D;C:>=07>;C T 28I8< ?>@V2=O=> 7 4>@>A;8<8 ?0FVT=B0<8. 0AB>AC20==O 4>7 100,
200 B0 400 <3 4>@>A;8< B0 4>7 3, 6 B0 12 <3/:3 4VBO< ?@872>48BL 4> 4>AO3=5==O A?V2AB02=>W
A8AB5<=>W 5:A?>78FVW.

D5:B82=VABL B0 157?5:0 70AB>AC20==O ?@5?0@0BC 4;O ;V:C20==O 35=VB0;L=8E :0=484>7V2 C
4VB59 =5 2AB0=>2;5=V, =572060NG8 =0 28G5@?>V 40=V I>4> 70AB>AC20==O ?@5?0@0BC \$;C=>;®
4VBO /:I> VA=CT =030;L=0 ?>B@510 70AB>AC20==O ?@5?0@0BC ?V4;VB:0< (2V:>< 2V4 12 4>
17 @>:V2), A;V4 70AB>A>2C20B8 728G09=V 4>78 4;O 4>@>A;8E.

VB8 2V:>< 2V4 5 4> 11 @>:V2.

0=484>78 A;87>28E >1>;>=: ?>G0B:>20 4>70 AB0=>28BL 6<3/:3/4>1C, ?V4B@870 3 <3/:3
/4>1C. >G0B:>2C 4>7C <>6=0 70AB>A>2C20B8 2 ?5@H89 45=L 7 <5B>N 1V;LH H284:>3> 4>AO3=5==O
@V2=>206=>W :=F5=B@0FVW.

=20782=V :0=484>78, :@8?B>:>:>289 <5=V=3VB: 4>70 ?@5?0@0BC AB0=>28BL 6-12 <3/:3/4>1C 70;56=>
2V4 ABC?5=O BO6:>ABV 70E2>@N20==O.

V4B@875@5465==O @5F8482C :@8?B>:>:>2>3> <5=V=3VBC C 4VB59 V7 28A>:8< @878:>< 9>3>
@>728B:C: 4>70 ?@5?0@0BC AB0=>28BL 6<3/:3/4>1C 70;56=> 2V4 ABC?5=O BO6:>ABV
70E2>@N20==O.

@>DV;0:B8:0 :0=484>7V2 C ?0FVT=BV2 7 V45DVF8B>70 ?@5?0@0BC AB0=>28BL

3-12 <3/:3/4>1C 70;56=> 2V4 28@065=>ABV B0 B@820;>ABV V=4C:>20=>W =59B@>?5=VW (482. 4>78
4;O 4>@>A;8E).

0FVT=B8 ;VB=L>3> 2V:C.

>7C =5>1EV4=> ?V418@0B8 70;56=> 2V4 AB0=C DC=:FV9 =8@>: (482. =86G5).

0FVT=B8 7 =8@>:>2>N =54>AB0B=VABN.

@8 @07>2>AC20==V :>@83C20B8 4>7C D;C:>=07>;C =5 ?>B@V1=>. 0FVT=B0< (2;:NG0NG8 4VB59)

V7 ?>@CH5==O< DC=:FV9 =8@>: ?@8 =5>1EV4=>ABV 1030B>@07>2>3> 70AB>AC20==O

?@5?0@0BC C ?5@H89 45=L ;V:C20==O A;V4 70AB>A>2C20B8 ?>G0B:>2C 4>7C 50-400<3 70;56=> 2V4
?>:070==O. VA;O FL>3> 4>1>2C 4>7C (70;56=> 2V4 ?>:070==O) A;V4 @>7@0E>2C20B8 2V4?>2V4=> 4>
=86G5=02545=>W B01;8FV:

;V@5=A :@50B8=V=C (<:/E2)	V4A>B>: 2V4 @5:><5=4>20=>W 4>78
> 50	100 %
≤ 50 (157 4V0;V7C)	50 %
53C;O@=89 4V0;V7	100 % ?VA;O :>6=>3> 4V0;V7C

0FVT=B8, O:V ?5@51C20NBL =0 @53C;O@=>28==V >B@8<5=4>20=>W 4>78 ?VA;O :>6=>3> 4V0;V7C.
45=L, :>;8 4V0;V7 =5 ?@>2>48BLAO, ?0FVT=B ?>28=5= >B@87C, 2V4:>@83>20=C 70;56=> 2V4
;V@5=AC :@50B8=V=C.

0FVT=B8 7 ?>@CH5==O< DC=:FV9 ?5GV=:8.

\$.C:>=07>; A;V4 70AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0< V7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8,
>A;V;L:8 V=D>@<0FVW I>4> 70AB>AC20==O D;C:>=07>;C FV9 :0B53>@VW ?0FVT=BV2
=54>AB0B=L>.

VB8.

0AB>A>2C20B8 ;V:0@AL:89 70AV1 C D>@@VW ?0FVT=BV2 <>6=0 B>4V, :>;8 4VB8 740B=V 157?5G=>
?@>:>2B=CB8 :0?AC;C, I> 70728G09 <>6;82> C 2V4V 2V4 5 @>:V2.

5@54>7C20==O.

B@8<0=> ?>2V4<>;5==O ?@> ?5@54>7C20==O D;C:>=07>;><; >4=>G0A=> ?>2V4<>;O;>AO ?@>
30;NF8=0FVW B0 ?0@0=>W40;L=C ?>254V=:C.

@8 ?5@54>7C20==V =5>1EV4=> ?@>25AB8 A8<0B8G=C ?V4B@81EV4=>ABV ?@><8B8 H;C=>:.

\$.C:>=07>; 7=0G=>N N 5:A:@5BCTBLAO 7 A5G5N; D>@A>20=89 4VC@57 <>65 ?@8A:>@8B8
282545==O ?@5?0@0BC. !50=A 35<>4V0;V7C B@820;VABN 3 3>48=8 7=86CT @V25=L D;C:>=07>;C C
?;072V ?@81;87=> =0 50 %.

>1VG=V @50:FVW.

09G0ABVH8<8 ?>1VG=8<8 @50:FVO<8 (> 1/10) T 3>;>2=89 1V;L, 1V;L C G5@52=V9 ?>@6=8=V,
4V0@50, =C4>B0, 1;N20==O, 28A8?0==O, ?V428I5==O @V2=O 0;0=V=0B@0=AD5@078 (!), 0A?0@B0B0
B@0=AD5@078 (!) B0 ;C6=>W D>AD0B078 :@>2V.

;O >FV=:8 G0AB>B8 28=8:=5==O ?>1VG=8E @50:FV9 28:>@8AB>2CNBL =0ABC?=C ;0A8DV:0FVN:
4C65 G0AB> (≥ 1/10), G0AB> (≥ 1/100 V < 1/10), =5G0AB> (≥ 1/1000 V < 1/100), @V4:> (≥ 1/10000 V < 1
/1000), 4C65 @V4:> (< 1/10000), B0 G0AB>B0 =52V4><0 (=5<>6;82> >FV=8B8 =0 ?V4AB02V =0O2=8E
40=8E).

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8.

5G0AB>: 0=5

V4>: 03@0=C;>F8B>7, ;59:>?5=VO, =59B@>?5=VO, B@><1>F8B>?5=VO.

I>:C VW A8AB5<8.

V4>: 0=0DV;0:AVO.

5B0I>;VG=V B0 0;V<5=B0@=V @>7;048.

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

V4>: 3V?5@B@83;VF5@845;5AB5@8=5:0;VT

A8EVG=V ?>@CH5==O.

5G0AB>: 157A>==O, A>=;82VABL.

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

'0AB>: 3>;>2=89 1V;L.

5G0AB>: AC4><8, 70?0<>@>G5==O, ?0@5AB57VW, ?>@CH5==O A<0:C.

V4>: B@5<>@.

I>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC.

5G0AB>: 25@B83>.

I>:C A5@F52>-AC48==>W A8AB5<8.

V4>: ?0@>:A87<0;L=0 H;C=>G:>20 B0EV:0@4VO B8?C «?V@C5B», ?>4>265==O V=B5@20;C QT.

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

'0AB>: 1V;L C G5@52=V9 ?>@>6=8=V, 4V0@50, =C4>B0, 1;N20==O.

5G0AB>: 70?>@, 48A?5?AVO, <5B5>@87<, ACEVABL C @>BV.

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

'0AB>: ?V428I5==O @V2=O 0;0=V=0B@0=AD5@078 (!), 0A?0@B0B0B@0=AD5@078 (!), ;C6=>W
D>AD0B078.

5G0AB>: E>;5AB07, 6>2BO=8FO, ?V428I5==O @V2=O 1V;V@C1V=C.

V4>: ?5GV=:>20 =54>AB0B=VABL, 35?0B>F5;N;O@=89 =5:@>7, 35?0B8B8, 35?0B>F5;N;O@=5
C@065==O.

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

'0AB>: 28A8?0==O.

5G0AB>: A25@1V6, <548:0<5=B>7=89 45@<0B8B, :@>?82O=:0, ?V428I5=5 ?>B>284V;5==O.

V4:>: B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, A8=4@<< !BV25=A0-6>=A>=0, 3>AB@89
35=5@0;V7>20=89 5:70=B5<0B>7=89 ?CABC;L>7, 5:AD>;V0B82=89 45@<0B8B, 0=3V>=52@>B8G=89
=01@O:, =01@O: >1;8GGO, 0;>?5FVO.

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

5G0AB>:

030;L=V @>7;048.

5G0AB>: ?V42815=0 2B><;N20=VABL, =574C60==O, 0AB5=VO, 30@OG:0.

VB8.

'0AB>B0 B0 E0@0:B5@ ?>1VG=8E @50:FV9 V 2V4E8;5=L 2V4 =>@<8 @57C;LB0BV2 ;01>@0B>@=8E
0=0;V7V2 C E>4V ;;V=VG=8E 4>A;V465=L 7 CG0ABN 4VB59 A?V2AB02=V 7 B0:8<8 C 4>@>A;8E.

"5@ABV.4 @>:8.

#<>28 715@V30==O.

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

15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 3 01> 7 :0?AC; C 1;VAB5@V, ?> 1 1;VAB5@C C :0@B>==V9 C?0:>2FV.

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

8@>1=8:.

'!'"' .(.

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

!0=:0:;0@ >CW 81100 <. N7465, "C@5GG8=0.