

!" #&/

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

\$#-/

!,:04:

4VNG0 @5G>28=0: 1 :0?AC;0 =07>;C 150 <3;

4>?>28=8: ;0:B>70, <=>3V4@0B; ;@>E<0;L :0@B>;O=89; ?>2V4>; ;0;LFVN AB50@0B;>1>;>=:0
:0?AC;8 4V0<0=B>289 A8=V9 (E 133), EV=>;V=>289 6>2B89 (E 104), 6>2B89 70EV4 FCF (110), B8B0=C
4V>:A84 (171), 65;0B8=, G>@=8;0 G>@=V (C @07V =0=5A5==O B>@3>2>3> 7=0:C ?V4?@8TGlaze 45 %
@>7G8= 2 5B0=>;V, 70;V70 >:A84 G>@=89 (172), ?@>?V;5=3;V>;L, 7G8= :>=F5=B@>20=89).

V:0@AL:0 D>@<0. 0?AC;8 B25@4V.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 7 =5?@>7>@8<8 :>@?CA>< V :@8H:>N
75;5=>3> :>;L>@C. 0 :0?AC;V 4>?CA:0TBLAO =0=>A8B8 B>20@=89 7=0: ?V4?@8T@>H>: 1V;>3> 7
6>2BC20B8< 2V4BV=;>< :>;L>@C. >?CA:0TBLAO =0O2=VABL 03;>5@0BV2 G0AB>: ?>@>H: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 "% J02!01.

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

\$0@<0:>48=0

5E0=V7< 4VW. \$;C:>=07>;, ?@>B83@81:>289 70AV1 :;0AC B@807>;V2 ?>BC6=89 A5;5:B82=89
V=3V1VB>@ 3@81:>28E D5@<5=BV2, =5>1EV4=8E 4;O A8=B57C 5@3>AB5@>;C. 5@28==8< <5E0=V7
<< 9>3> 4VW T ?@83=VG5==O 3@81:>2>3> 14-0;LD0-;0=>AB5@>;-45<5B8;N20==O,
>?>A5@54:>20=>3> F8B>E@><< 450 (CYP), I> T =52V4T<=8< 5B0?>< 1V>A8=B57C 3@81:>2>3>
5@3>AB5@>;C. :C @V7=8E A8AB5< D5@<5=BV2 F8B>E@>
0AB>AC20==O D;C:>=07>;C C 4>7V 50 <3 =0 4>1C ?@>B03>< 28 4=V2 =5 2?;820T =0 @V25=L
B5AB>AB5@>=C C ?;072V C G>;>2V:V2 B0 =0 @V25=L 5=4>35==8E AB5@>W4V2 C 6V=>;
@5?@>4C:B82=>3> 2V:C. \$;C:>=07>; C 4>7V 200-400 <3 =0 4>1C =5 ?@>O2;OT :;V=VG=> 7=0GCI>3>
2?;82C =0 @V25=L 5=4>35==8E AB5@>W4V2 01> =0 2V4?>2V4L =0 AB8>@B8:>B@>?=>3> 3>@<=<C
(") C 74>@>28E 4>1@>2>;LFV2 G>;>2VG>W AB0BV.

>A;V465==O 270T<>4VW 7 0=B8?V@8=>< ?@>45<=<AB@C20>;, I> 70AB>AC20==O 50 <3 D;C:>=07>;C
@07>2> 01> 1030B>@07>2> =5 2?;820T =0 <5B01>;V7< 0=B8?V@8=C.

'CB;82VABL *in vitro* \$;C:>=07>; *in vitro* 45<=<AB@CT ?@>B83@81:>2C 0:B82=VABL AB>A>2=> 284V2
Candida, I> 7CAB@VG0NBLAO =09G0ABVH5 (2;;NG0NG8 *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C.*
glabrata 45<=<AB@CT H8@>:89 4V0?07>= GCB;82>ABV 4> D;C:>=07>;C, B>4V O: *C. krusei* T 4> =L>3>
@578AB5=B=>N.

"0:>6 D;C:>=07>; *in vitro* 45<=<AB@CT 0:B82=VABL O: ?@>B8 *Cryptococcus neoformans* B0 *Cryptococcus*
gattii, B0: V ?@>B8 5=45*Blastomices dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* B0
Paracoccidioides brasiliensis.

5E0=V7< @578AB5=B=>ABV. V:@>>@30=V7<8 @>4C *Candida* <0NBL G8A;5==V <5E0=V7<8
@578AB5=B=>ABV 4> 07>;L=8E ?@>B83@81:>28E 70A>1V2. \$;C:>=07>; 45<=<AB@CT 28A>:C
<0NBL >48= 01> 1V;LH5 <5E0=V7ABV, I> =530B82=> 2?;820T =0 5D5:B82=VABLin *vivo* B0 C
:;V=VG=V9 ?@0:B8FV. >2V4>;O;>AO ?@> 28?04:8 @>728B:C AC?5@V=D5:FVW *Candida spp.*, V=H8
<8, =V6 *C. albicans* 2840<8, I> G0AB> T =5GCB;828<8 4> D;C:>=07>;C (=0?@8:;04, *C. :rusei*). ;O
;V:C20==O B0:8E 28?04:V2 A;V4 70AB>A>2C20B8 0;LB5@=0B82=V ?@>B83@81:>2V 70A>18.
\$0@<0:>:V=5B8:0. \$0@<0:>:V=5B8G=V 2;0AB82>ABV D;C:>=07>;C T ?>4V1=8<8 ?@8
2=CB@VH=L>25==>@0;L=>AC20==V.

1A>@1FVO. \$;C:>=07>; 4>1@5 2A<:BCTBLAO ?@8 ?5@>@0;L=>AC20==V, 0 @V25=L ?@5?0@0BC C
?;072V V A8AB5<=0 1V>4>ABC?=VABL ?5@528ICNBL 90% @V2=O D;C:>=07>;C C ?;072V, I>
4>AO30TBLAO ?@8 2=CB@VH=L>25==>G0A=5 26820==O W6V =5 2?;820T =0 2A<:BC20==O
?@5?0@0BC ?@8 9>3> ?5@>@0;L=>AC20==V. V:>20 :>=F5=B@0FVO C ?;072V 4>AO30TBLAO G5@57
0,5-1,5 3>48=8 ?VA;O ?@89>F5=B@0FVO ?@5?0@0BC C ?;072V ?@>?>@FV9=0 4> 4>78. V2=>206=0

:>=F5=B@0FVO =0 @V2=V 90 % 4>AO30TBLAO =0 4@C389 45=L ;V:C20==O ?@8 70AB>AC20==V C
?5@H89 45=L =020=B06C20;L=>W 4>78, I> 242VGV ?5@528ICT 728G09=C 4>1>2C 4>7C.
>7?>4V; . 1T< @>7?>4V;C ?@81;87=> 4>@V2=NT 7030;L=>@30=V7 %).
\$;C:>=07>; 4>1@5 ?@>=8:0T 2 CAV 4>A;V46C20=V @V48=8 >@30=V7=07>;C C A;8=V B0 <:@>B8==V
T ?>4V1=8< 4> :>=F5=B@0FVW ?@5?0@0BC C ?;072V. # ?0FVT=BV2, E2>@8E =0 3@81:>289
<5=V=3VB, @V25=L D;C:>=07>;C C A?8==<>7:>2V9 @V48=V 4>AO30T 80 % :>=F5=B@0FVW C ?;07
2V.
8A>:V :>=F5=B@0FVW D;C:>=07>;C C H:V@V, I> ?5@528ICNBL A8@>20B:>2V, 4>AO30NBLAO C
@>3>2>BV. \$;C:>=07>; =0:>?8GCTBLAO C @>3>2>
V>B@0=AD>@<0FVO. \$;C:>=07>; <5B01>;V7CTBLAO =57=0G=>N N. @8 22545==V 4>78, W
@04V>0:B82=8<8 V7>B>?0<8, ;8H5 11 % D;C:>=07>;C 5:A:@5BCTBLAO 7 A5G5N C 7=07>; T A5;5:B82=8
< V=3V1VB>@>< V7>D5@<5=BV2 CYP2!9 B0 CYP34, 0 B0:>6 V=3V1VB>@>< V7>D5@<5=BC
CYP2!19.
:A:@5FVO. " 1/2 D;C:>=07>;C V7 ?;07<8 :@>2V AB0=>28BL 1;87L:> 303>48=. V;LH0 G0AB8=0
?@5?0@0BC 282>48BLAO =8@:0<8, ?@8G> % 70AB>A>20=>W 4>78 28O2;OTBLAO C A5GV C =57
=07>;C ?@>?>@FV9=89 4> ;V@5=AC :@50B8=V=C. ?NNG8E <5B01>;V7V2 =5 28O2;5=>.
"@820;89 " 1/2 ?@5?0@0BC 7 ?;07<8 :@>2V 40T <>6;82VABL @07>2>3> 70AB>AC20==O ?@5?0@0BC
?@8 203V=0;L=>7V, 0 B0:>6 70AB>AC20==O ?@5?0@0BC 1 @07 =0 B8645=L ?@8 V=H8E ?>:070==OE.
8@:>20 =54>AB0B=VABL.# ?0FVT=BV2 V7 =8@:>2>N =54>AB0B=VABN B06:>3> ABC?5=O
(H284:VABL ;C1>G:>2>W DV;LB@0FVW < 20<:/E2) " 1/2 71V;LHCTBLAO 7 303>48= 4> 983>48=. ">
@VW ?0FVT=BV2 =5>1EV4=> 7<5=H8B8 4>7C D;C:>=07>;C. \$;C:>=07>; 2840;OTBLAO H;OE>< 35
<>4V0;V7C, <5=H>N N H;OE>< V=B@0?5@8B>=50;L=>3> 4V0;V7C. !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 %.
0FVT=B8 ;VB=L>3> 2V:C.

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

>:070==O. >AB@89 203V=0;L=89 :0=484>7, :0=484>7=89 10;0=VB (:>;8 FV;L=>N).

@>B8?>:070==O. V?5@GCB;82VABL 4> :>5=BV2 ?@5?0@0BC/V=H8E 07>;L=8E A?>;C:. 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. 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=5 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. 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=: G5@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. @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. 0AB>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;: ACAC20==O D;C:>=07>;C B0 0AB5;C <>65 7<5=H8B8 ;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=: ACAC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C <>65 ?@872>48B8 4> ?@83=VG5==O <5B01>;V72V <>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 ?V428ICT @878: @>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»), O: =0A;V4>: <>6;820 @0?B>20 A5@F520 A<5@BL. 0AB>AC20==O :><1V=0FVW F8E ;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=: D;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 ?V428ICT @878: @>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»), O: =0A;V4>: <>6;820 @0?B>20 A5@F520 A<5@BL. !;V4 C=8:0B8 70AB>AC20==O :><1V=0FVW F8E ;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>; ;V=VG=> 7=0GCI>3> 2?;82C =0 01A>@1FVN D;C:>=07>;C ?@8 9>3> ?5@>@0;L=>AC20==V =5 <0NBL >4=>G0A=89 ?@89< W6V, F8<5B848=, 0=B0F848, 0 B0:>6 ?@><5=520 B5@0?VO CAVTW 4V;O=:8 BV;0 (?@8 ?5@5A04FV :VAB:>2>3<>7:C). 8D0 >4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 @8D048;> 4> 7=865==O AUC =0 25 % B0 A:>@>GC20;> "1/2 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>@<< CYP2C9 B0 ?> 2V :>=F5=B@0FV9 V=H8E A?>;C:, I><5B01>;V7CNBLAO CYP2C9 B0 CYP3A4, ?@8 >4=>G0A=> AC20==V WE V7 D;C:>=07>;>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. # 7207:C 7 B@820;8< "1/2 D;C:>=07>;C 9>3> ?@83=VGC20;L=0 4VO =0 D5@<5=B8 715@V30TBLAO ?@>BO3<< 4-5 4V1. ;LD5=B0=V; :>4=>G0A=5 70AB>AC20==O D;C:>=07>;C C 4>7V 400 <3 B0 0;LD5=B0=V;C C 4>7V 20 2>46CTBLAO 42>:@0B=8< 71V;LH5==O< ?>:07=8:0 AUC10 (<>6;82>, G5@57 V=3V1C20==O CYP3A4). &5 7C<>2;NT =5>1EV4=VABL C :>@83C20==V 4>78 0;LD5=B0=V;C. , =>@B@8?B8;V=: D;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 ?VA;O WW ?>G0B:C. # @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< 40;> B0:V @57C;LB0B8: =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 A. fumigatus. ;V=VG=5 7=0G5==O F8E @57C;LB0BV2 =52V4<<5. =B8:>03C;O=B8: O: 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><0, =>A>20 :@>2>B5G0, H;C=:>2>:8H:>20 :@>2>B5G0, 35<0BC@VO B0 <5;5=0) =0 B;V ?>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 "1/2 C 3,7 B0 2,2 @07C 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 "1/2 C 4,4 B0 2,3 @07C 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=: D;C:>=07>; ?@83=VGCT <5B01>;V7< :0@10<075?V=C B0 A?@8G8=OT ?V428I5==O
@V2=O :0@10<075?V=C C 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;LFVT28E :0=0;V2: 45O:V 0=B03>=VAB8 :0;LFVN (=VD548?V=, VA@048?V=, 0<;>48?V= B0
D5;>48?V=) <5B01>;V7CNBLAO D5@<5=B>< CYP3A4. \$;C:>=07>; <>65 ?V428IC20B8 A8AB5<=C
5:A?>78FVN 1;>:0B>@V2 :0;LFVT28E :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) V F5;5:>:A81C (200 <3) 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 C A8@>20BFV :@>2V. &V ?@5?0@0B8<>6=0 70AB>A>2C20B8
>4=>G0A=>, 0;5 A;V4 2@0E>2C20B8 @878: ?V428I5==O :>=F5=B@0FVW 1V;V@C1V=C B0
:@50B8=V=C C A8@>20BFV :@>2V.
\$5=B0=V;: ?>2V4><;O;>AO ?@> >48= ;5B0;L=89 28?04>: 2=0A;V4>: V=B>:A8:0FVW D5=B0=V;×
G5@57 <>6;82C 270T<>4VN < B0 D;C:>=07>;>=07>; 7=0G=> C?>2V;L=NT 5;V=F5=B@0FVW D5=B0=V;C
<>65 ?@872>48B8 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: ACAC20==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. # @07V 7=0G=>3> ?V428I5==O @V2=O
:@50B8=:V=078, 0 B0:>6 ?@8 ?V4>7@V G8 28O2;5==V ?0BVW/@014>;V7C 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=: D;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 @07C. &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 D;C:>=07>; <>65 ?V428IC20B8 :>=F5=B@0FVN 525@>;V20BFV :@>2V G5@57 ?@83=VG5==O
CYP34.
!8@>;V: D;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 2V4 ?@89>
"0:@>;V D;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=86C20B8 70;56=> 2V4 :>=F5=B@0FVW B0:@>;V
>70@B0=: D;C:>=07>; ?@83=VGCT ?5@5B2>@5==O ;>70@B0=C 4> 9>3> 0:B82=>3> <5B01>;VBC
(E-31 74). 5:>5=4>20=> 74V9A=N20B8 ?>ABV9=89 <=VB>@8=3 0@B5@V0;L=>3> B8A:C C
?0FVT=BV2.
5B04>=: D;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=>AC20==V
D;C:>=07>;C 7 @0F5 <3) C_{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 2V4?>2V4=8<8 ?>:07=8:0<8 ?@8
70AB>AC20==V BV;L:8 @0F53> V1C?@>D5=C.

\$;C:>=07>; ?>B5=FV9=> 740B=89 ?V428IC20B8 A8AB5<=C 5:A?>78FVN V=H8E =5AB5@>W4=8E
?@>B870?0;L=8E ?@5?0@0BV2 (), I> <5B01>;V7CNBLAO CYP2C9 (=0?@8::04 =0?@>:A5=C,
B>:A8G=8E ?@>O2V2, ?>2O70=8E V7 . >65 ?>B@51C20B8AO :>@83C20==O 4>78 .
\$5=VB>W=: D;C:>=07>; ?@83=VGCT <5B01>;V7< D5=VB>W=C C ?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> ?@8A:>@5==O <5B01>;V7=C. !;V4
@5B5;L=> AB568B8 70 ?0FVT=B0<8, O:V ?@>BO3< 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=: D;C:>=07>; ?V428ICT :>=F5=B@0FVN @8D01CB8=C C 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 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@: D;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=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:>4=>G0A=5 70AB>AC20==O D;C:>=07>;C V7 ?5@>@0;L=8<8 ?>EV4=8
<8 AC;LD>=V;A5G>28=8 (E;>@?@>?Q1CB048;> 4> ?@>;>=3C20==O WE "1/2. 5:><5=4CTBLAO
?@>2>48B8 G0AB89 :>=B@>;L FC:@C C :@>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=: 70AB>AC20==O D;C:>=07>;C ?> 200 <3 ?@>BO3<< 14 4=V2 ?@8725;> 4> 7=865==O
A5@54=L>3> ;V@5=AC B5>DV;V=C C ?;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: B>:A8G=>W 4VW B5>DV;V=C.
"5@0?VN A;V4 7O2V >7=0: B>:A8G=>ABV.
;:0;> W48 10@2V=:C: 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 ?;072V (=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 F5=B@0;L=>W
=5@2>2>W A8AB5<8 (&!) C D>@BC<>@C 3>;>2=>3> <>7:C, I> 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 B0 CYP34): >4=>G0A=5 70AB>AC20==O 2>@8:>=07>;C
?5@>@0;L=> (?> 400 <3 :>6=V 12 3>48= ?@>BO3<< 1 4=O, ?>BV< ?> 200 <3 :>6=V 12 3>48= ?@>BO3<<
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
?@>BO3<< 4 4=V2) ?@8725;> 4> ?V428I5==O !_{max} B0 AUC_τ 2>@8:>=07>;C C A5@54=L> 57 % (90 % : 20
%, 107 %) B0 79 % (90 % : 40 %, 128 %) 2V4?>2V4=>. 52V4><>, G8 7=865==O 4>78 B0/01> G0AB>B8
70AB>AC20==O 2>@8:>=07>;C 01> D;C:>=07>;C CAC20T B0:89 5D5:B. @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=: D;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. "1/2
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@> ?@8 >4=>G0A=>@0;L=>2>AC20==V 078B@>=07>;C C 4>70E 1200 <3 B0 800 <3 2V4?>2V4=>
6>4=8E 7=0GCI8E D0@<0>:V=5B8G=8E 270T<>4V9 28O2;5=> =5 1C;>.
5@>@0;L=V :>=B@0F5?B828: ?@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>DVBVO. □V4><>, I> ?@8 70AB>AC20==V D;C:>=07>;C 4;O ;V:C20==O 45@<0B>DVBVW C
4VB59 >AB0==V9 =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 %. ">=07>;=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.
;8I>: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 (482. @>74V; <!>?>AV1 70AB>AC20==O B0 4>78»).
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=BV2 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@V30NBLAO 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=BV2 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@02V4><;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 D;C:>=07>;C.
"0:V ?>2V4><;5==O AB>AC20;8AO ?0FVT=BV2 V7 BO6:8<8 70E2>@N20==O<8 ?@8 ?>T4=0==V
1030BL>E D0:B>@V2 @878:C, B0:8E O: AB@C:BC@=V 70E2>@N20==O A5@FO, ?>@CH5==O
5;5:B@>;VB=>3> >14=>G0A=5 70AB>AC20==O V=H8E ;V:0@AL:8E 70A>1V2, I> 2?;820NBL =0
V=B5@20; Q".
\$;C:>=07>;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, ?@>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=A06>=A>=0 B0 A8=4@<
09T;;0. 0FVT=B8, E2>@V =0 !, 1V;LH AE8;L=V 4> @>728B:C BO6:8E H:V@=8E @50:FV9 ?@8
70AB>AC20==V 1030BL>E ;V:0@AL:8E 70A>1V2. /:I> C ?0FVT=B0 V7 ?>25@E=52>N 3@81:>2>N
V=D5:FVTN 7O2;ONBLAO 28A8?8, 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. /:I> C ?0FVT=B0 7 V=20782=>N/A8AB5<=>N
3@81:>2>N V=D5:FVTN 7O2;ONBLAO 28A8?8 =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?V2 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.
CYP. \$;C:>=07>; T ?>BC6=8< V=3V1VB>@>< D5@<5=BC CYP2C9 B0 ?>
"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.
@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, A8=4@><< 3;N:>7>-30;0:B>7=>W
<0;L01A>@1FVW.

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) :V;L:< A>B=O< 203VB=8E
6V=>: ?@>BO3>< I B@8<5AB@C 203VB=>ABV, =5 ?@>45<=>AB@C20;8 =51060=8E 5D5:BV2 =0 ?;V4.
>2V4><;O;>AO ?@> G8A;5==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)
?@>BO3>< ?@8=09<=V B@L>E 01> 1V;LH5:F84i>W4>7C. 207>: AC20==O< D;C:>=07>;C B0 F8<8
28?04:0<8 =5 287=0G5=89.
>A;V465==O =0 B20@8=0E ?@>45<=>AB@C20;8 @5?@>4C:B82=C B>:A8G=VABL.
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> 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 2?;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 2?;82C D;C:>=07>;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. @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. 0?AC;8 A;V4 :>2B0B8 FV;8<8. @89>< ?@5?0@0BC =5 70;568BL 2V4
?@89>
>@>A;V. @5?0@0B 70AB>A>2C20B8 ?5@>@0;L=> C 4>7V 150 <3 >4=>@07>2>.
0FVT=B8 ;VB=L>3> 2V:C. @8 2V4ACB=>ABV >7=0: ?>@CH5==O DC=:FV9 =8@>: 4;O ;V:C20==O
FVTW :0B53>@VW ?0FVT=BV2 70AB>A>2C20B8 728G09=C 4>7C 4;O 4>@>A;8E.
>@CH5==O DC=:FV9 =8@>: \$;C:>=07>; 282>48BLAO 2 >A=>2=>2>AC20==V ?@5?0@0BC
:>@83C20B8 4>7C FV9 :0B53>@VW ?0FVT=BV2 =5 ?>B@V1=>.
>@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. 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 D;C:>=07>;C 4VBO
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.

5@54>7C20==O.

!8<8: 30;NF8=0FVW B0 ?0@0=>W40;L=0 ?>254V=:0.

V:C20==O: A8<0B8G=5 (C B><820==O H;C=:0 V ?V4B@8=07>; 282>48BLAO 2 >A=>2=>@A>20=89
4VC@57 <>65 ?@8A:>@8B8 282545==O ?@5?0@0BC. !50=A 35<>4V0;V7C B@820;VABN 33>48=8
7=86CT @V25=L D;C:>=07>;C C ?;072V ?@81;87=> =0 50 %.

>1VG=V @50:FVW.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 0=5F8B>7, ;59:>?5=VO, =59B@>?5=VO, B@><1>F8B>?5=VO.

I>:C VW A8AB5<8: 0=0DV;0:AVO.

5B0I>;VG=V B0 0;V<5=B0@=V @>7;048: 7=865==O 0?5B8BC, 3V?5@B@83;VF5@845;5AB5@8=5:0;VT
A8EVG=V ?>@CH5==O: 157A>==O, A>=;82VABL.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, AC4<8, 70?0<>@>G5==O, ?0@5AB57VW, ?>@CH5==O A
<0:C, B@5<>@.

I>:C >@30=V2 A;CEC B0 25AB8IC;O@=>3> 0?0@0BC: 25@B83>.

I>:C A5@FO: ?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: 1V;L C G5@52=V9 ?>@>6=8=V, 4V0@5O, =C4>B0, 1;N20==O,
70?>@, 48A?5?AVO, <5B5>@87<, ACEVABL C @>BV.

5?0B>1V;V0@=V @>7;048: ?V428I5==O @V2=O 0;0=V=0B@0=AD5@078 (!), 0A?0@B0B0
B@0=AD5@078 (!), ;C6=>W D>AD0B078, E>;5AB07, 6>2BO=8FO, ?V428I5==O @V2=O 1V;V@C1V=C,
?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: 28A8?0==O, A25@1V6, <548:0<5=B>7=89 45@<0B8B,
:@>?82O=:0, ?V428I5=5 ?>B>284V;5==O, A8=4@< 09T;;0, A8=4@< !BV25=A06>=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:

030;L=V @>7;048: ?V428I5=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 ?>@V2=O==V 7 B0:8<8 C 4>@>A;8E.

"5@ABV.5 @>:V2.

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

#?0:>2:0. 0?AC;0 1 C 1;VAB5@V C :>@>1FV.

0B53>@VO 2V4?CA:C. 57 @5F5?B0.

8@>1=8:. ">20@8AB2> 7 >1<565=>N 2V4?>2V40;L=VABN «\$0@<0F52B8G=0 :>@>2□O».

VAf57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.

#: @0W=0, 61013,

!" #&/

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

\$#-/

!,:04:

4VNG0 @5G>28=0: 1 :0?AC;0 =07>;C 50 <3 01> 100 <3, 01> 150 <3;
4>?>28=8: ;0:B>70, <=>3V4@0B; :@>E<0;L :0@B>;O=89; ?>2V4>; :0;LFVN AB50@0B;>1>;>=:0
:0?AC;8 @>8;0 G>@>V (C @07V =0=5A5==O B>@3>2>3> 7=0:C ?V4?@8TGlaze 45 % @>7G8= 2
5B0=>;V, 70;V70 >:A84 G>@>89 (172), ?@>?V;5=3;V>;L, 07G8= :>=F5=B@>20=89) (2AV 4>7C20==O),
B8B0=C 4V>:A84 (171), 65;0B8= (4>7C20==O 50 <3) 01> B8B0=C 4V>:A84 (171), 5@8B@>78= (127),
EV=>;V=>289 6>2B89 (104), 65;0B8= (4>7C20==O 100 <3) 01> 4V0<0=B>289 A8=V9 (E 133), EV=>;V=>289
6>2B89 (E 104), 6>2B89 70EV4 FCF (110), B8B0=C 4V>:A84 (171), 65;0B8= (4>7C20==O 150 <3).

V:0@AL:0 D>@<0. 0?AC;8 B25@4V.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 7 =5?@>7>@8<8 :>@?CA>< V :@8H:>N 1V;>3>
:>;L>@C (4>7C20==O 50 <3) 01> 6>2B>3> :>;L>@C (4>7C20==O 100 <3), 01> 75;5=>3> :>;L>@C
(4>7C20==O 150 <3). 0 :0?AC;V 4>?CA:0TBLAO =0=>A8B8 B>20@>89 7=0: ?V4?@8T@>H>: 1V;>3> 7
6>2BC20B8< 2V4BV=:>< :>;L>@C. >?CA:0TBLAO =0O2=VABL 03;>5@0BV2 G0AB>: ?>@>H: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 "% J02!01.

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

\$0@<0:>48=0

5E0=V7< 4VW. \$;C:>=07>;, ?@>B83@81:>289 70AV1 :;0AC B@807>;V2 ?>BC6=89 A5;5:B82=89
V=3V1VB>@ 3@81:>28E D5@<5=BV2, =5>1EV4=8E 4;O A8=B57C 5@3>AB5@>;C. 5@28==8< <5E0=V7
<< 9>3> 4VW T ?@83=VG5==O 3@81:>2>3> 14-0;LD0-;0=>AB5@>;-45<5B8;N20==O,
>?>A5@54:>20=>3> F8B>E@><< 450 (CYP), I> T =52V4T<=8< 5B0?>< 1V>A8=B57C
3@81:>2>3> 5@3>AB5@>;C. :C @V7=8E A8AB5< D5@<5=BV2 F8B>E@>
0AB>AC20==O D;C:>=07>;C C 4>7V 50 <3 =0 4>1C ?@>BO3>< 28 4=V2 =5 2?;820T =0 @V25=L
B5AB>AB5@>=C C ?;072V C G>;>2V:V2 B0 =0 @V25=L 5=4>35==8E AB5@>W4V2 C 6V=>:
@5?@>4C:B82=>3> 2V:C. \$;C:>=07>; C 4>7V 200-400 <3 =0 4>1C =5 ?@>O2;OT :;V=VG=> 7=0GCI>3>
2?;82C =0 @V25=L 5=4>35==8E AB5@>W4V2 01> =0 2V4?>2V4L =0 AB8>@B8:>B@>?=>3> 3>@<=>C
(") C 74>@>28E 4>1@>2>;LFV2 G>;>2VG>W AB0BV.
>A;V465==O 270T<>4VW 7 0=B8?V@8=>< ?@>45<=>AB@C20>;, I> 70AB>AC20==O 50 <3 D;C:>=07>;C
@07>2> 01> 1030B>@07>2> =5 2?;820T =0 <5B01>;V7< 0=B8?V@8=C.
'CB;82VABL *in vitro* \$;C:>=07>; *in vitro* 45<=>AB@CT ?@>B83@81:>2C 0:B82=VABL AB>A>2=> 284V2
Candida, I> 7CAB@VG0NBLAO =09G0ABVH5 (2;;NG0NG8 *C. albicans*, *C. parapsilosis*, *C. tropicalis*. *C.*
glabrata 45<=>AB@CT H8@>:89 4V0?07>= GCB;82>ABV 4> D;C:>=07>;C, B>4V O: *C. krusei* T 4> =L>3>
@578AB5=B=>N.

"0:>6 D;C:>=07>; *in vitro* 45<=>AB@CT 0:B82=VABL O: ?@>B8 *Cryptococcus neoformans* B0 *Cryptococcus*
gattii, B0: V ?@>B8 5=45*Blastomices dermatitidis* *Coccidioides immitis*, *Histoplasma capsulatum* B0
Paracoccidioides brasiliensis.

5E0=V7< @578AB5=B=>ABV. V:@>>@30=V7<8 @>4C *Candida* <0NBL G8A;5==V <5E0=V7<8
@578AB5=B=>ABV 4> 07>;L=8E ?@>B83@81:>28E 70A>1V2. \$;C:>=07>; 45<=>AB@CT 28A>:C
<0NBL >48= 01> 1V;LH5 <5E0=V7ABV, I> =530B82=> 2?;820T =0 5D5:B82=VABL *in vivo* B0 C
:;V=VG=V9 ?@0:B8FV. >2V4>;O;>AO ?@> 28?04:8 @>728B:C AC?5@V=D5:FVW *Candida spp.*, V=H8
<8, =V6 *C. albicans* 2840<8, I> G0AB> T =5GCB;828<8 4> D;C:>=07>;C (=0?@8::04, *C. :rusei*). ;O
;V:C20==O B0:8E 28?04:V2 A;V4 70AB>A>2C20B8 0;LB5@>0B82=V ?@>B83@81:>2V 70A>18.
\$0@<0:>:V=5B8:0. \$0@<0:>:V=5B8G=V 2;0AB82>ABV D;C:>=07>;C T ?>4V1=8<8 ?@8
2=CB@VH=L>25==>@0;L=>AC20==V.

1A>@1FVO. \$;C:>=07>; 4>1@5 2A<:BCTBLAO ?@8 ?5@>@0;L=>AC20==V, 0 @V25=L ?@5?0@0BC C
?;072V V A8AB5<=0 1V>4>ABC?=VABL ?5@528ICNBL 90% @V2=O D;C:>=07>;C C ?;072V, I>
4>AO30TBLAO ?@8 2=CB@VH=L>25==>G0A=5 26820==O W6V =5 2?;820T =0 2A<:BC20==O
?@5?0@0BC ?@8 9>3> ?5@>@0;L=>AC20==V. V:>20 :>=F5=B@0FVO C ?;072V 4>AO30TBLAO G5@57
0,5-1,5 3>48=8 ?VA;O ?@89>F5=B@0FVO ?@5?0@0BC C ?;072V ?@>?>@FV9=0 4> 4>78. V2=>206=0

:>=F5=B@0FVO =0 @V2=V 90 % 4>AO30TBLAO =0 4@C389 45=L ;V:C20==O ?@8 70AB>AC20==V C
?5@H89 45=L =020=B06C20;L=>W 4>78, I> 242VGV ?5@528ICT 728G09=C 4>1>2C 4>7C.
>7?>4V;.: 1T< @>7?>4V;C ?@81;87=> 4>@V2=NT 7030;L=>@30=V7 %).
\$;C:>=07>; 4>1@5 ?@>=8:0T 2 CAV 4>A;V46C20=V @V48=8 >@30=V7=07>;C C A;8=V B0 <: @>B8==V
T ?>4V1=8< 4> :>=F5=B@0FVW ?@5?0@0BC C ?;072V. # ?0FVT=BV2, E2>@8E =0 3@81:>289
<5=V=3VB, @V25=L D;C:>=07>;C C A?8==<>7:>2V9 @V48=V 4>AO30T 80 % :>=F5=B@0FVW C ?;07
2V.
8A>:V :>=F5=B@0FVW D;C:>=07>;C C H:V@V, I> ?5@528ICNBL A8@>20B:>2V, 4>AO30NBLO C
@>3>2>BV. \$;C:>=07>; =0:>?8GCTBLAO C @>3>2>
V>B@0=AD>@<0FVO. \$;C:>=07>; <5B01>;V7CTBLAO =57=0G=>N N. @8 22545==V 4>78, W
@04V>0:B82=8<8 V7>B>?0<8, ;8H5 11 % D;C:>=07>;C 5:A:@5BCTBLAO 7 A5G5N C 7=07>; T A5;5:B82=8
< V=3V1VB>@>< V7>D5@<5=BV2 CYP2!9 B0 CYP34, 0 B0:>6 V=3V1VB>@>< V7>D5@<5=BC
CYP2!19.
:A:@5FVO. " 1/2 D;C:>=07>;C V7 ?;07<8 :@>2V AB0=>28BL 1;87L:> 303>48=. V;LH0 G0AB8=0
?@5?0@0BC 282>48BLAO =8@:0<8, ?@8G> % 70AB>A>20=>W 4>78 28O2;OTBLAO C A5GV C =57
=07>;C ?@>?>@FV9=89 4> ;V@5=AC :@50B8=V=C. ?NNG8E <5B01>;V7V2 =5 28O2;5=>.
"@820;89 "1/2 ?@5?0@0BC 7 ?;07<8 :@>2V 40T <>6;82VABL @07>2>3> 70AB>AC20==O ?@5?0@0BC
?@8 203V=0;L=>7V, 0 B0:>6 70AB>AC20==O ?@5?0@0BC 1 @07 =0 B8645=L ?@8 V=H8E ?>:070==OE.
8@:>20 =54>AB0B=VABL.# ?0FVT=BV2 V7 =8@:>2>N =54>AB0B=VABN B06:>3> ABC?5=O
(H284:VABL ;C1>G:>2>W DV;LB@0FVW < 20<;E2) "1/2 71V;LHCTBLAO 7 303>48= 4> 98 3>48=. ">
@VW ?0FVT=BV2 =5>1EV4=> 7<5=H8B8 4>7C D;C:>=07>;C. \$;C:>=07>; 2840;OTBLAO H;OE>< 35
<>4V0;V7C, <5=H>N N H;OE>< V=B@0?5@8B>=50;L=>3> 4V0;V7C. !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 %.
0FVT=B8 ;VB=L>3> 2V:C.

;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;

:>:F84V>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 01> @5F8482=89, :>;8 FV;L=>N;

:0=484>7=89 10;0=VB, :>;8 FV;L=>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 T =54>FV;L=>N;

45@<0B>DVB=89 =>VE>7, :>;8 70AB>AC20==O V=H8E ;V:0@AL:8E 70A>1V2 T =54>FV;L=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 -V=DV:>20=8E ?0FVT=BV2 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:);

:0=484>7=V V=D5:FVW C ?0FVT=BV2 V7 B@820;>N =59B@>?5=VTN (=0?@8::04, ?0FVT=B8 7V

7;>O:VA=8<8 70E2>@N20==O<8 :@>2V, O:V >B@8B5@0?VN, ?0FVT=B8 ?@8 B@0=A?;0=B0FVW 35

<>?>5B8G=8E AB>21C@>28E ;VB8=).

VB8. 0AB>A>2C20B8 ;V:0@AL:89 70AV1 C D>@>@>:V2.

@5?0@0B 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>< <>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> :>5=BV2 ?@5?0@0BC/V=H8E 07>;L=8E A?>;C:. 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. 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=5 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. 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=: G5@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. @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. 0AB>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;: ACAC20==O D;C:>=07>;C B0 0AB5;C <>65 7<5=H8B8 ;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=: ACAC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C <>65 ?@872>48B8 4>
?@83=VG5==O <5B01>;V72V <>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 ?V428ICT @878: @>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»), O: =0A;V4>: <>6;820 @0?B>20 A5@F520 A<5@BL. 0AB>AC20==O :><1V=0FVW F8E
;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=: D;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 ?V428ICT
@878: @>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»), O: =0A;V4>: <>6;820 @0?B>20 A5@F520 A<5@BL. !;V4 C=8:0B8
70AB>AC20==O :><1V=0FVW F8E ;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>;: ;V=VG=> 7=0GCI>3> 2?;82C =0 01A>@1FVN
D;C:>=07>;C ?@8 9>3> ?5@>@0;L=>AC20==V =5 <0NBL >4=>G0A=89 ?@89< W6V, F8<5B848=,
0=B0F848, 0 B0:>6 ?@><5=520 B5@0?VO CAVTW 4V;O=:8 BV;0 (?@8 ?5@5A04FV :VAB:>2>3><>7:C).
8D0 >4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 @8D048;> 4> 7=865==O AUC =0 25 % B0
A:>@>GC20;> "½ 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>@>< CYP2C9 B0 ?>
 2V :=F5=B@0FV9 V=H8E A?>;C:, I><5B01>;V7CNBLAO CYP2C9 B0 CYP3A4, ?@8 >4=>G0A=>
 AC20==V WE V7 D;C:>=07>;>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. # 7207:C 7 B@820;8< "1/2 D;C:>=07>;C
 9>3> ?@83=VGC20;L=0 4VO =0 D5@<5=B8 715@V30TBLAO ?@>BO3<< 4-5 4V1.
 ;LD5=B0=V;.: >4=>G0A=5 70AB>AC20==O D;C:>=07>;C C 4>7V 400 <3 B0 0;LD5=B0=V;C C 4>7V 20
 2>46CTBLAO 42>:@0B=8< 71V;LH5==O< ?>:07=8:0 AUC10 (<6;82>, G5@57 V=3V1C20==O CYP3A4).
 &5 7C<>2;NT=5>1EV4=VABL C :=@83C20==V 4>78 0;LD5=B0=V;C.
 , =>@B@8?B8;V=: D;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 ?VA;O WW
 ?>G0B:C. # @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< 40;> B0:V @57C;LB0B8: =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 A. fumigatus. ;V=VG=5 7=0G5==O F8E @57C;LB0BV2 =52V4><5.
 =B8:>03C;O=B8: O: 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><0, =>A>20 :@>2>B5G0, H;C=:>2>-.8H:>20 :@>2>B5G0, 35<0BC@VO B0 <5;5=0) =0 B;V
 ?>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 "1/2 C 3,7 B0 2,2 @07C 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 "1/2
 C 4,4 B0 2,3 @07C 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;04 70
 AB0=<< ?0FVT=B0.
 0@10<075?V=: D;C:>=07>; ?@83=VGCT <5B01>;V7< :0@10<075?V=C B0 A?@8G8=OT ?V428I5==O
 @V2=O :0@10<075?V=C C 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;LFVT28E :0=0;V2: 45O:V 0=B03>=VAB8 :0;LFVN (=VD548?V=, VA@048?V=, 0<;>48?V= B0
 D5;>48?V=) <5B01>;V7CNBLAO D5@<5=B>< CYP3A4. \$;C:>=07>; <>65 ?V428IC20B8 A8AB5<=C
 5:A?>78FVN 1;>:0B>@V2 :0;LFVT28E :0=0;V2. 5:<<5=4>20=89 @5B5;L=89 <=>VB>@8=3 I>4>
 @>728B:C ?>1VG=8E @50:FV9.
 ?5.:>:A81: ?@8 >4=>G0A=>AC20==V D;C:>=07>;C (200 <3 =0 4>1C) V F5;5>:A81C (200 <3) Cmax 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 C A8@>20BFV :@>2V. &V ?@5?0@0B8<>6=0 70AB>A>2C20B8
 >4=>G0A=>, 0;5 A;V4 2@0E>2C20B8 @878: ?V428I5==O :=F5=B@0FVW 1V;V@C1V=C B0
 :@50B8=V=C C A8@>20BFV :@>2V.
 \$5=B0=V;.: ?>2V4><;O;>AO ?@> >48= ;5B0;L=89 28?04>: 2=0A;V4>: V=B>:A8:0FVW D5=B0=V;<
 G5@57 <>6;82C 270T<>4VN < B0 D;C:>=07>;>=07>; 7=0G=> C?>2V;L=NT 5;V=F5=B@0FVW D5=B0=V;C
 <>65 ?@872>48B8 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: ACAC20==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. # @07V 7=0G=>3> ?V428I5==O @V2=O
 :@50B8=:V=078, 0 B0:>6 ?@8 ?V4>7@V G8 28O2;5==V ?0BVW/@014>;V7C 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=: D;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@07C. &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 D;C:>=07>; <>65 ?V428IC20B8 :>=F5=B@0FVN 525@>;V20BFV :@>2V G5@57 ?@83=VG5==O
 CYP34.
 !8@>;V: D;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 2V4 ?@89>
 "0:@>;V D;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=86C20B8 70;56=> 2V4 :>=F5=B@0FVW B0:@>;V
 >70@B0=: D;C:>=07>; ?@83=VGCT ?5@5B2>@5==O ;>70@B0=C 4> 9>3> 0:B82=>3> <5B01>;VBC
 (E-31 74). 5:>5=4>20=> 74V9A=N20B8 ?>ABV9=89 <=>VB>@8=3 0@B5@V0;L=>3> B8A:C C
 ?0FVT=BV2.
 5B04>=: D;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=>AC20==V
 D;C:>=07>;C 7 @0F5 <3) C_{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 2V4?>2V4=8<8 ?>:07=8:0<8 ?@8
 70AB>AC20==V BV;L:8 @0F53> V1C?@>D5=C.
 \$;C:>=07>; ?>B5=V9=> 740B=89 ?V428IC20B8 A8AB5<=C 5:A?>78FVN V=H8E =5AB5@>W4=8E
 ?@>B870?0;L=8E ?@5?0@0BV2 (), I> <5B01>;V7CNBLAO CYP2C9 (=0?@8:;04 =0?@>:A5=C,
 ;>@>=:A8:0D5=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 ?>B@51C20B8AO :>@83C20==O 4>78 .
 \$5=VB>W=: D;C:>=07>; ?@83=VGCT <5B01>;V7< D5=VB>W=C C ?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> ?@8A:>@5==O <5B01>;V7=C. !;V4
 @5B5;L=> AB568B8 70 ?0FVT=B0<8, O:V ?@>BO3< 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=: D;C:>=07>; ?V428ICT :>=F5=B@0FVN @8D01CB8=C C 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 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@: D;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=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:>4=>G0A=5 70AB>AC20==O D;C:>=07>;C V7 ?5@>@0;L=8<8 ?>EV4=8
<8 AC;LD>=V;A5G>28=8 (E;>@?@?Q1CB048;> 4> ?@>;>=3C20==O WE "1/2. 5:><5=4CTBLAO
?@>2>48B8 G0AB89 :>=B@>;L FC:@C C :@>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=: 70AB>AC20==O D;C:>=07>;C ?> 200 <3 ?@>BO3<< 14 4=V2 ?@8725;> 4> 7=865==O
A5@54=L>3> :;V@5=AC B5>DV;V=C C ?;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;O4 I>4> 28O2;5==O >7=0: B>:A8G=>W 4VW B5>DV;V=C.
"5@0?VN A;V4 7O2V >7=0: B>:A8G=>ABV.
;:0;>W48 10@2V=:C: 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 ?;072V (=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 F5=B@0;L=>W
=5@2>2>W A8AB5<8 (&!) C D>@BC<>@C 3>;>2=>3> <>7:C, I> 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 B0 CYP34): >4=>G0A=5 70AB>AC20==O 2>@8:>=07>;C
?5@>@0;L=> (?> 400 <3 :>6=V 12 3>48= ?@>BO3<< 1 4=O, ?>BV< ?> 200 <3 :>6=V 12 3>48= ?@>BO3<<
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
?@>BO3<< 4 4=V2) ?@8725;> 4> ?V428I5==O !_{max} B0 AUC_τ 2>@8:>=07>;C C A5@54=L> 57 % (90 % : 20
%, 107 %) B0 79 % (90 % : 40 %, 128 %) 2V4?>2V4=>. 52V4><>, G8 7=865==O 4>78 B0/01> G0AB>B8
70AB>AC20==O 2>@8:>=07>;C 01> D;C:>=07>;C CAC20T B0:89 5D5:B. @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=: D;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. "1/2
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@> ?@8 >4=>G0A=>@0;L=>2>AC20==V 078B@>=07>;C C 4>70E 1200 <3 B0 800 <3 2V4?>2V4=>
6>4=8E 7=0GCI8E D0@<0>:V=5B8G=8E 270T<>4V9 28O2;5=> =5 1C;>.
5@>@0;L=V :>=B@0F5?B828: ?@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@04 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>DVBVO. □V4><>, I> ?@8 70AB>AC20==V D;C:>=07>;C 4;O ;V:C20==O 45@<0B>DVBVW C
4VB59 >AB0==V9 =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 %. ">=07>;=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 (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»).

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 B06:>W 35?0B>B>:A8G=>ABV, 2;:NG0NG8 ;5B0;L=V 28?04:8, 3>;>2=8

< G8=>< C ?0FVT=BV2 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@V30NBLAO 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=BV2 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@02V4><;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 D;C:>=07>;C.
"0:V ?>2V4><;5==O AB>AC20;8AO ?0FVT=BV2 V7 BO6:8<8 70E2>@N20==O<8 ?@8 ?>T4=0==V
1030BL>E D0:B>@V2 @878:C, B0:8E O: AB@C:BC@=V 70E2>@N20==O A5@FO, ?>@CH5==O
5;5:B@>;VB=>3> >14=>G0A=5 70AB>AC20==O V=H8E ;V:0@AL:8E 70A>1V2, I> 2?;820NBL =0
V=B5@20; Q".
\$;C:>=07>;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, ?@>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=A06>=A>=0 B0 A8=4@<
09T;;0. 0FVT=B8, E2>@V =0 !, 1V;LH AE8;L=V 4> @>728B:C BO6:8E H:V@=8E @50:FV9 ?@8
70AB>AC20==V 1030BL>E ;V:0@AL:8E 70A>1V2. /:I> C ?0FVT=B0 V7 ?>25@E=52>N 3@81:>2>N
V=D5:FVTN 702;ONBLAO 28A8?8, 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. /:I> C ?0FVT=B0 7 V=20782=>N/A8AB5<=>N
3@81:>2>N V=D5:FVTN 702;ONBLAO 28A8?8 =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?V2 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.
CYP. \$;C:>=07>; T ?>BC6=8< V=3V1VB>@< D5@<5=BC CYP2C9 B0 ?>
"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.
@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, A8=4@<<< 3;N:>7>-30;0:B>7=>W
<0;L01A>@1FVW.

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) :V;L:< A>B=O< 203VB=8E
6V=>: ?@>BO3<< I B@8<5AB@C 203VB=>ABV, =5 ?@>45<=>AB@C20;8 =51060=8E 5D5:BV2 =0 ?;V4.
>2V4><;O;>AO ?@> G8A;5==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)
?@>BO3<< ?@8=09<=V B@L>E 01> 1V;LH5 :F84i>W4>7C. 207>: AC20==O< D;C:>=07>;C B0 F8<8
28?04:0<8 =5 287=0G5=89.
>A;V465==O =0 B20@8=0E ?@>45<=>AB@C20;8 @5?@>4C:B82=C B>:A8G=VABL.
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> 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 2?;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 2?;82C D;C:>=07>;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. @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. @5?0@0B 70AB>A>2C20B8 ?5@>@0;L=>. @89>< ?@5?0@0BC =5
70;568BL 2V4 ?@89>**

>1>20 4>70 D;C:>=07>;C 70;568BL 2V4 284C B0 BO6:>ABV 3@81:>2>W V=D5:FVW.@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.

>@>A;8

@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>=095=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 4>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=484B@8<0==O =530B82=8E @57C;LB0BV2
?>AV2C :@>2V B0 7=8:=5==O >7=0: V A88BL 2 B86=V.

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 7-2145=L (4> 4>AO3=5==O @5, 0;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=O. ;O ?0FVT=BV2
V7 BO6:8< V45DVF8B>< B@820;VABL ;V:C20==O<>65 1CB8 71V;LH5=0.

%@>=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 >1>;>=>: @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> ?@8 7=865==V 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
>4=>@07>2>.
V:C20==O B0 ?@>DV;0:B8:0 @5F8482=8E 203V=0;L=8E :0=484>7V2 (4 01> 1V;LH5 @5F8482V2
70E2>@N20==O =0 @V:): @5:<5=4>20=0 4>70 AB0=>28BL 150 <3 1 @07 C 3 4=V. #AL>3> A;V4
70AB>AC20B8 3 4>78 (1-9 45=L, 4-9 45=L B0 7-9 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 =5 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 V 70;568BL 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>@>: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. @5?0@0B 70AB>A>2C20B8 1 @07 =0 4>1C.
>7C20==O ?@5?0@0BC 4;O 4VB59 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. @0E>2CNG8 <0AC BV;0 48B8=8 B0 ?C15@B0B=89 @>728B>: ;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. @8 70AB>AC20==V 4>7 100, 200 B0 400 <3 4>@>A;8< B0 4>7 3, 6 B0 12 <3/:3 4VBO<
4>AO30TBLAO ?>@V2=O==0 A8AB5<=0 5:A?>78FVO.
D5:B82=VABL B0 157?5:0 70AB>AC20==O D;C:>=07>;C 4;O ;V:C20==O 35=VB0;L=8E :0=484>7V2 C
4VB59 =5 2AB0=>2;5=V. /: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 C ?5@H89 45=L 7 <5B>N H284H>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@8?5@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 B5@0?52B8G=8E ?>:070=L. 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:

$;V@5=A:@50B8=V=C(<./E2)$	$V4A>B>:2V4@5:><5=4>20=>W4>78$
>50	100%
$\leq 50(1574V0;V7C)$	50%
$53C;O@=894V0;V7$	$100\%?VA;O:>6=>3>4V0;V7C$

0FVT=B8, O:V ?5@51C20NBL =0 @53C;O@=>28==V >B@8 % @5:><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>@

5@54>7C20==O.

!8<8: 30;NF8=0FVW B0 ?0@0=>W40;L=0 ?>254V=:0.

V:C20==O: A8<0B8G=5 (C B><820==O H;C=:0 V ?V4B@8=07>; 282>48BLAO 2 >A=>2=>@A>20=89 4VC@57 <>65 ?@8A:>@8B8 282545==O ?@5?0@0BC. !50=A 35<>4V0;V7C B@820;VABN 33>48=8 7=86CT @V25=L D;C:>=07>;C C ?;072V ?@81;87=>=0 50 %.

>1VG=V @50:FVW.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 0=5F8B>7, ;59:>?5=VO, =59B@>?5=VO, B@><1>F8B>?5=VO.

I>:C VW A8AB5<8: 0=0DV;0:AVO.

5B0I>;VG=V B0 0;V<5=B0@=V @>7;048: 7=865==O 0?5B8BC, 3V?5@B@83;VF5@845;5AB5@8=5:0;VT A8EVG=V ?>@CH5==O: 157A>==O, A>=;82VABL.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, AC4<8, 70?0<>@>G5==O, ?0@5AB57VW, ?>@CH5==O A <0;C, B@5<>@.

I>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC: 25@B83>.

I>:C A5@FO: ?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: 1V;L C G5@52=V9 ?>@>6=8=V, 4V0@5O, =C4>B0, 1;N20==O, 70?>@, 48A?5?AVO, <5B5>@87<, ACEVABL C @>BV.

5?0B>1V;V0@=V @>7;048: ?V428I5==O @V2=O 0;0=V=0B@0=AD5@078 (!), 0A?0@B0B0 B@0=AD5@078 (!), ;C6=>W D>AD0B078, E>;5AB07, 6>2B0=8FO, ?V428I5==O @V2=O 1V;V@C1V=C, ?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: 28A8?0==O, A25@1V6, <548:0<5=B>7=89 45@<0B8B, :@>?82O=:0, ?V428I5=5 ?>B>284V;5==O, A8=4@< 09T;;0, A8=4@< !BV25=A06>=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:

030;L=V @>7;048: ?V428I5=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 ?>@V2=O==V 7 B0:8<8 C 4>@>A;8E.

"5@ABV.5 @>:V2.

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

#?0:>2:0.0?AC;8 ?> 50 <3 01> 100 <3 7, 10 C 1;VAB5@V C :>@>1FV 01> ?> 150<3 1□2, 1□3, 3, 7 C
1;VAB5@V C :>@>1FV.

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

8@>1=8:.. ">20@8AB2> 7 >1<565=>N 2V4?>2V40;L=VABN «\$0@<0F52B8G=0 :>@>2□O».

VAf57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.
#:@0W=0, 61013,