

!" #&/
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

!#25, !#50, !#100
(SUPERVIGA 25, SUPERVIGA 50, SUPERVIGA 100)

!;:04:

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

1 B01;5B:0

4>?>28=8: F5;N;>70 :@8AB0;VG=0; :0;LFDVN 3V4@>D>AD0B 1572>4=89; 0;N:A84; =0B@VN :@>A:0@<5;>70; ?>2V4>=; <03=VN AB50@0B; :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89; ACE0 AC«Opadry II white», I> :A84 (171), B0;L.; ?>;V5B8;5=3;V>;L (<0:@>3>);, A?8@B ?>;V2V=V;>289; V=483>:0@:0=4C@8= «!@V1=89 1;8A:».

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

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, I> 70AB>A>2CNBLAO ?@8 5@5:B8;L=V9 48ADC=:FVW.
!8;45=0DV;. >4 "I G04B E03.

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

>:070==O. @5?0@0B @5:><5=4CTBLAO 70AB>A>2C20B8 G>;>2V:0< V7 5@5:B8;L=>N 48ADC=:FVTN,
O:0 287=0G0TBLAO O: =5740B=VABL 4>AO3B8 01> ?V4B@8<0B8 5@5:FVN AB0B52>3> G;5=0,
=5>1EV4=C 4;O CA?VH=>3> AB0B52>3> 0:BC.
;O 5D5:B82=>W 4VW ?@5?0@0BC ?>B@V1=5 A5:AC0;L=5 71C465==O.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> 0:B82=>W @5G>28=8 01> 1C4L-O:>W 7 4>?>28= ?@5?0@0BC.
4=>G0A=5 70AB>AC20==O V7 4>=>@0<8 >:A84C 07>BC (B0:8<8 O: 0 =VB@0B0<8 C 1C4L-O:V9 D>@B8?>:070=5, >A:V;L:8 2V4><>, I> A8;45=0DV;<0T 2?;82 =0 H;OE8 <5B01>;V7:A84C 07>BC/F8;;VG=>3>3C0=>78=<<=>D>AD0BC (F\$) B0 ?>B5=VNT 3V?>B5=782=89 5D5:B =VB@0BV2.
!B0=8, ?@8 O:8E =5 @5:><5=4>20=0 A5:AC0;L=0 0:B82=VABL (=0?@8;:04, BO6:V A5@F52>-AC48==V @>7;048, B0:V O: =5AB01V;L=0 AB5=>:0@4VO 01> A5@F520 =54>AB0B=VABL BO6:>3> ABC?5=O).
B@0B0 7>@C =0 >4=5 >:> 2=0A;V4>: =50@B5@V0;L=>W ?5@54=L>W VH5W =52@>?0BVW 7>@>2>3>=5@20 =570;56=> 2V4 B>3>, ?>2O70=0 FO ?0B>;>3VO V7 ?>?5@54=V< 70AB>AC20==O<V=3V1VB>@V2 \$5 G8 =V.
0O2=VABL B0:8E 70E2>@N20=L, O: ?>@CH5==O DC=:FVW ?5GV=:8 BO6:>3> ABC?5=O,
0@B5@V0;L=0 3V?>B5=7VO (0@B5@V0;L=89 B8A: =86G5 90/50 << @B. AB.), =5I>402=> ?5@5=5A5=89
V=AC;LB 01> V=D0@:B :0@40 B0 2V4>2V 4535=5@0B82=V 70E2>@N20==O AVB:V2:8, B0:V O: ?V3
<5=B=89 @5B8=VB (=525;8:0 :V;L:VABL B0:8E ?0FVT=V2<0T 35=5B8G=V @>7;048
D>AD>4V5AB5@07 AVB:V2:8), >A:V;L:8 157?5:0 A8;45=0DV;C =5 4>A;V46C20;0AO C B0:8E
?V43@C?0E ?0FVT=V2.

!?!>AV1 70AB>AC20==O B0 4>78. @5?0@0B 70AB>A>2C20B8 ?5@>@0;L=>.

>@>A;V. 5:><5=4>20=0 4>70 ?@5?0@0BC AB0=>28BL 50<3 B0 70AB>A>2CTBLAO C @07V
=5>1EV4=>ABV ?@81;87=> 70 3>48=C 4> A5:AC0;L=>W 0:B82=>ABV. 0;56=> 2V4 5D5:B82=>ABV B0
?5@5=>A8<>ABV ?@5?0@0BC 4>7C <>6=0 71V;LH8B8 4> 100 <3 01> 7=878B8 4> 25 <3. 0:A8<0;L=0
@5:><5=4>20=0 4>70 AB0=>28BL 100 <3. '0AB>B0 70AB>AC20==O <0:A8<0;L=>W @5:>
<5=4>20=>W 4>78 ?@5?0@0BC AB0=>28BL
1 @07 =0 4>1C. @8 70AB>AC20==V ?@5?0@0BC ?V4 G0A ?@89>
0FVT=B8 ;VB=L>3> 2V:C. 5>1EV4=VABL C :>@5:FVW 4>78 ?0FVT=B0< ;VB=L>3> 2V:C (≥ 65 @>:V2)
2V4ACB=O.
0FVT=B8 V7 =8@:>2>N =54>AB0B=VABN. 0FVT=B0< V7 =8@:>2>N =54>AB0B=VABN ;53:>3> B0 ?>3>
ABC?5=O BO6:>ABV (:;V@5=A :@50B8=V=C 30-80 <;/E2) @5:><5=4>20=0 4>70 ?@5?0@0BC T B0:>N 6,
O: =02545=> 28I5 C ?V4@>74V;V <<@>A;V».

A:V;L:8 C ?0FVT=BV2 7 =8@:>2>N =54>AB0B=VABN BO6:>3> ABC?5=O (:;V@5=A :@50B8=V=C <30
<:/E2) :;V@5=A A8;45=0DV;C 7=865=89, A;V4 @>73;O=CB8<>6;82VABL 70AB>AC20==O 4>78 25<3.
0;56=> 2V4 5D5:B82=>ABV B0 ?5@5=>A8<>ABV ?@5?0@0BC ?@8 =5>1EV4=>ABV 4>7C <>6=0
71V;LH8B8 ?>ABC?>2> 4> 50<3 B0 4> 100 <3.

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

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

<5B>N

>1VG=V @50:FVW.

=D5:FV9=V B0 V=20782=V 70E2>@N20==O: @8=VB.

I>:C VW A8AB5<8: 3V?5@GCB;82VABL.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O, A>;82VABL, 3V?5AB57VO, V=AC;LB,
B@0=78B>@=0 VH5<8, @5F84828 AC4<, A8=:>?5, 0B0:AVO, =52@0;3VO, =59@>?0BVO,
?0@5AB57VO, B@5<>@, 25@B83>, 45?@5AVO, 157A>==O, 0=×0;L=V A=>284V==O, 7=865==O
@5D;5:AV2, B@82>30, B@0=78B>@=0 3;>10;L=0 0<=57VO.

I>:C >@30=V2 7>@C: ?>@CH5==O A?@89=OBBO :>;L>@C (E;>@>?AVO, E@×0B>?AVO,
FV0=>?AVO, 5@8B@>?AVO, :A0=B>?AVO), @>7;048 7>@C, 70B<0@5==O 7>@C, @>7;048
A;L>7>284V;5==O (ACEVABL 2 >G0E, ?>@CH5==O A;L>7>284V;5==O B0 ?V428I5==O
A;L>7>284V;5==O), 1V;L 2 >G0E, D>B>D>1VO, D>B>?AVO, 3V?5@5G59, OA:@02VABL 7>@C,
:=N=:B82VB, >;N7VO AC48= AVB:V2:8, @5B8=0;L=89 :@>2>28;82, 0@B5@V>A:;5@>B8G=0
@5B8=>?0BVO, ?>@CH5==O 7 1>:C AVB:V2:8, 3;0C:×0, 45D5:B8 ?>;O 7>@C, 48?;>?VO, 7=865==O
3>AB@>B8 7>@C, ?VO, 0AB5=>?VO, ?;020NGV ?>284=>3> BV;0, ?>@CH5==O 7 1>:C @094C6=>W
>1>;=:8, O20 AONG8E :@C3V2 =02:>;> 465@5;0 A2VB;0 (30;>) C ?>;V 7>@C, =01@O: >G59,
?@8?CE;VABL >G59, ?>@CH5==O 7 1>:C >G59, 3V?5@5=N=:B828, ?>4@07=5==O >G59, 0=><0;L=V
2V4GCBBO 2 >G0E, =01@O: ?>2V.;, 7=510@2;5==O A:;5@8, :@>2>28;82 2 >:, :0B0@0:B0, ACEVABL 2
>G0E, B820 2B@0B0 7>@C, ?>G5@2>=V==O >G59, ?5GVO 2 >G0E, ?V428I5==O 2=CB@VH=L>>G=>3>
B8A:C, =01@O: AVB:V2:8, AC48==V 70E2>@N20==O AVB:V2:8 G8 :@>2>B5G0, 2V4H0@C20==O
A:;>?>4V1=>3> BV;0.

>2V4><;O;>AO ?@> 28?04:8 =50@B5@V0;L=>W ?5@54=L>W VH5W =59@>?0BVW 7>@>2>3> =5@20,
I> T ?@8G8=>N 7=865==O 7>@C, 2;;NG0NG8 ?>ABV9=C 2B@0BC 7>@C, O:V 1C;8 ?>2O70=V C G0AV
V7 70AB>AC20==O< V=3V1VB>@V2 \$5, 2;;NG0NG8 A8;45=0DV;. 030B> 7 ?0FVT=BV2, 0;5 =5 2AV;<0;8
=0O2=V 0=0B> AC48==V D0:B>@8 @878:C @>728B:C =50@B5@V0;L=>W ?5@54=L>W VH5W
=59@>?0BVW 7>@>2>3> =5@20, 2;;NG0NG8 (0;5 =5>1>2O7:>2> >1<56CNG8AL) B0:V: =87L:5
A?V22V4=>H5==O 4V0<5B@C 5:A:020FVW B0 48A:C 7>@>2>3> =5@20 (70ABV9=89 48A: 7>@>2>3>
=5@20), 2V: 1V;LH5 =V6 50 @>:V2, 3V?5@B5=7VO, 70E2>@N20==O :>@>=0@=8E 0@B5@V9,
3V?5@;V?V45

I>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC: 472V= C 2CE0E, 3;CE>B0, 1V;L C 2CE0E.
>2V4><;O;>AO ?@> 28?04:8 @0?B>2>3> 7=865==O G8 2B@0B8 A;CEC, ?>2O70=V C G0AV V7
70AB>AC20==O< A8;45=0DV;C. # 45O:8E 28?04:0E ?>2V4<;O;>AO ?@> =0O2=VABL <548G=8E
AB0=V2 B0 V=H8E D0:B>@V2, I> <>3;8 2V4V3@0B8 @>;L C @>728B:C ?>1VG=8E @50:FV9 7 1>:C
A;CEC. # 1030BL>E 28?04:0E V=D>@<0FVO I>4> ?>40;LH>3> <548G=>3> A?>AB5@565==O
2V4ACB=O. 87=0G8B8, G8 FV O28I0 ?@O<> ?>2O70=V V7 70AB>AC20==O< A8;45=0DV;C, 7 =0O2=8<8
D0:B>@0<8 @878:C 2B@0B8 A;CEC, 7 :<1V=0FVTN F8E D0:B>@V2 G8 7 V=H8<8 D0:B>@0<8, =5
<>6;82>.

I>:C A5@FO: B0EV:0@4VO, ?>A8;5=5 A5@F518BBO, @0?B>20 A5@F520 A<5@BL, V=D0@:B :0@40, H;C=>G:>20 0@8B:0@4VO, AB5=>:0@4VO, V-1;>:040, VH5:0@40, @0?B>20 7C?8=:0 A5@FO, ?>@CH5==O @57C;LB0BV2 =0 , :0@4V>?0BVO.

I>:C AC48=: ?@8;828 :@>2V, ?@8;828 :@>2V 4>>1;8GGO, ?@8;828 60@C, 3V?5@B5=7VO, 3V?>B5=7VO, ABC@0;L=0 3V?>B5=7VO, B@><1>7 AC48= 3>;>2=>3> <>7:C.

>2V4><;O;>AO ?@> A5@9>7=V A5@F52>-AC48==V, F5@51@>20A:C;O@=V B0 AC48==V O28I0, 2;;NG0NG8 F5@51@>20A:C;O@=C :@>2>B5GC, AC10@0E=>W40;L=C B0

2=CB@VH=L>F5@51@0;L=C :@>2>B5GC B0 ;535=52C :@>2>B5GC, I> 1C;8 ?>2070=V C G0AV V7 70AB>AC20==O< A8;45=0DV;C. V;LHVABL ?0FVT=BV2, 0;5 =5 2AV<0;8 VA=CNGV D0:B>@8 A5@F52>-AC48==>3> @878:C. >2V4><;O;>AO, I> 1030B> 7 F8E O28I 28=8;;8 ?V4 G0A 01> 2V4@07C ?VA;O A5:AC0;L=>W 0:B82=>ABV, B0 45:V;L:0 O28I 28=8;;8 2V4@07C ?V4 G0A 70AB>AC20==O A8;45=0DV;C 157 A5:AC0;L=>W 0:B82=>ABV. =HV O28I0 28=8;;8 ?@>BO3< =0ABC?=8E 3>48= G8 4=V2 ?VA;O 70AB>AC20==O A8;45=0DV;C B0 A5:AC0;L=>W 0:B82=>ABV. 5>6;82> 2AB0=>28B8, G8 <0NBL FV O28I0 ?@O<89 72O7>: V7 70AB>AC20==O< A8;45=0DV;C, V7 A5:AC0;L=>N 0:B82=VABN, V7 =0O2=8<8 D0:B>@0<8 @878:C G8 7 :><1V=0FVTN F8E D0:B>@V2, G8 7 V=H8<8 D0:B>@0<8.

I>:C @5A?V@0B>@=>W A8AB5<8, 3@C4=>W ;;VB:8 B0 A5@54>ABV==O: 70;;045=VABL =>A0, =>A>20 :@>2>B5G0, 70;;045=VABL ?@840B:>28E ?07CE =>A0, 2V4GCBBO AB8A=5==O C 3>@;V, =01@O: A;87>2>W >1>;>=:8 =>A0, ACEVABL C =>AV, 0AB0, 48A?=>5, ;0@8=3VB, D0@8=3VB, A8=CA8B, 1@>=EVB, ?>A8;5=5 A;8=>284V;5==O, ?>A8;5==O :0H;N.

I>:C H;C=:>2>-.8H:>2>3> B@0:BC: =C4>B0, 48A?5?AVO, 30AB@>57>D0350;L=0 @5D;N:A=0 E2>@>10, 1;N20==O, 1V;L C 25@E=V9 G0AB8=V 682>B0, ACEVABL C @>BV, 3V?5AB57VO @>B>2>W ?>@>6=8=8, 3;>A8B, :>;VB, 48AD03VO, 30AB@8B, 30AB@>5=B5@8B, 57>D03VB, AB<0B8B, ?>@CH5==O @57C;LB0BV2 ?5GV=:>28E ?@>1, @5:B0;L=0 :@>2>B5G0, 3V=3V2VB.

I>:C H:V@8 B0 ?V4H:V@=>W B:0=8=8: 28A8?0==O, A8=4@<< !BV25=A0-6>=A>=0, A8=4@<< 09T;;0, :@>?82O=:0, 35@?5A, A25@1V6, ?VB;82VABL, 28@07:8 H:V@8, :>=B0:B=89 45@<0B8B, 5:AD>;V0B82=89 45@<0B8B.

I>:C >?>@=>-@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8: 7, @>7@82 ACE>68;;O, B5=>A8=>2VB, 1V;L C :VAB:0E,2VB.

I>:C A5G>284V;L=>W A8AB5<8: 35<0BC@VO, F8AB8B, =V:BC@VO, ?V428I5=0 G0AB>B0 A5G>28?CA:0=L, =5B@8<0==O A5GV.

I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: :@>2>B5G0 7V AB0B52>3> G;5=0, ?@V0?V7 <, 35<0B>A?5@4>265=0 5@5:FVO, 71V;LH5==O <>;>G=8E 70;>7, ?>@CH5==O 5O:C;OFVW, =01@O: AB0B528E >@30=V2, 0=>@307

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

>2V4><;O;>AO ?@> @>728B>: 207>>;N782=8E :@87V2, I> ?>B@51C20;8 3>A?VB0;V70FVW, ?@8 70AB>AC20==V A8;45=0DV;C ?0FVT=B0< 7 ;535=52>N 0@B5@V0;L=>N 3V?5@B5=7VTN, 2B>@8==>N I>4> A5@?>?>4V1=>;;VB8==>W 0=5@<0FVW 4;O ?0FVT=BV2, O:V 70AB>A>2CNBL ?@5?0@0B 7 <5B>N ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW, T =52V4<8

>7;048 <5B01>;V7A?@030, =01@O.; ?>403@0, =5AB01V;L=89 4V015B, 3V?5@3;V:53;V:5 030;L=V @>7;048 B0 @50:FVW C 1V;L C 3@C4OE, ?V428I5=0 AB<;N20=VABL, 2V4GCBBO 60@C, ?>4@07=5==O, =01@O: >1;8GGO, @50:FVW D>B>GCB;82>ABV, H>;, 0AB5=VO, 1V;L, @0?B>25 ?04V==O, 1V;L C 682>BV, @0?B>25 ?>H:>465==O, 1V;L C A?8=V.

IAB565==O: ?V428I5=0 G0AB>B0 A5@F528E A:>@>G5=L.

2VBC20==O ?@> ?V4>7@N20=V ?>1VG=V @50:FVW. 2VBC20==O ?@> ?V4>7@N20=V ?>1VG=V @50:FVW ?VA;O @5TAB@0FVW ;V:0@AL:>3> 70A>1C<0T 206;825 7=0G5==O. &5 40T 7<>3C ?@>2>48B8 157?5@5@2=89 <=>VB>@8=3 A?V22V4=>H5==O @8ABN V @878:0<8, ?>2070=8<8 V7 70AB>AC20==O< FL>3> ;V:0@AL:>3> 70A>1C. V:0@O< A;V4 72VBC20B8 ?@> 1C4L-O:V ?V4>7@N20=V ?>1VG=V @50:FVW 2V4?>2V4=> 4> 28<>3 70:>=>402AB20.

5@54>7C20==O. V4 G0A 70AB>AC20==O @07>2>W 4>78 A8;45=0DV;C 4> 800<3 ?>1VG=V @50:FVW 1C;8 ?>4V1=8<8 4> B8E, I> A?>AB5@V30;8AO ?@8 70AB>AC20==V A8;45=0DV;C C =86G8E 4>70E, 0;5 7CAB@VG0;8AO G0ABVH5 B0 1C;8 1V;LH B06:8<8. 0AB>A>2C20==O A8;45=0DV;C C 4>7V 200<3 =5 ?@872>48;> 4> ?V428I5==O 5D5:B82=>ABV, 0;5 A?@8G8=O;> 7@>AB0==O :V;L:>ABV 28?04:V2 @>728B:C ?>1VG=8E @50:FV9 (3>;>2=>3> 1>;N, ?@8;82V2 :@>2V, 70?0<>@>G5==O, 48A?5?AVW, 70;;045=>ABV =>A0, ?>@CH5=L 7 1>:C >@30=V2 7>@C).

@07V ?5@54>7C20==O ?@8 =5>1EV4=>ABV 240B8AO 4> 728G09=8E ?V4B@84V2. @8A:>@5==O
::V@5=AC A8;45=0DV;C ?@8 35<>4V0;V7V <0;>9<>2V@=5 2=0A;V4>: 28A>:>3> ABC?5=O
7207C20==O ?@5?0@0BC 7 1V;:0<8 ?;07<8 :@>2V B0 2V4ACB=>ABV 5;V

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N. @5?0@0B =5 ?@87=0G5=89 4;O
70AB>AC20==O 6V=:0<8.

VB8. @5?0@0B =5 ?>:070=89 4> 70AB>AC20==O >A>10<8 2V:<> 4> 18 @>:V2.

A>1;82>ABV 70AB>AC20==O. > ?>G0B:C B5@0?VW A;V4 7V1@0B8 <548G=89 0=0<=57 ?0FVT=B0 B0
?@>25AB8 DV78:0;L=5 >1AB565==O 4;O 4V03=>AB8:8 5@5:B8;L=>W 48ADC=:FVW B0 287=0G5==O
WW <>6;828E ?@8G8=.

\$0:B>@8 @878:C A5@F52>-AC48==8E 70E2>@N20=L. A:V;L:8 A5:AC0;L=0 0:B82=VABL
AC?@>2>46CTBLAO ?52=8< @878:<> 7 1>:C A5@FO, 4> ?>G0B:C 1C4L-O:>3> ;V:C20==O
5@5:B8;L=>W 48ADC=:FVW ;V:0@<0T >FV=8B8 AB0= A5@F52>-AC48==>W A8AB5<8 ?0FVT=B0.
!8;45=0DV; G8=8BL AC48=>@>7H8@N20;L=C 4VN, I> ?@>O2;OTBLAO ;53:8< B0 :>@>B:>G0A=8<
7=865==O< 0@B5@V0;L=>3> B8A:C. > ?@87=0G5==O A8;45=0DV;C ;V:0@<0T @5B5;L=> 72068B8, G8
<>65 B0:89 5D5:B =5A?@8OB;82> 2?;820B8 =0 ?0FVT=BV2 V7 ?52=8<8 >A=>2=8<8 70E2>@N20==O<8,
>A>1;82> C :<<1V=0FVW V7 A5:AC0;L=>N 0:B82=VABN. > ?0FVT=BV2 V7 ?V428I5=>N GCB;82VABN
4> 207>48;OB0B>@V2 =0;560BL ?0FVT=B8 V7 >1AB@C:FVTN 282V4=>3> B@0:BC ;V2>3> H;C=>G:0
(=0?@8::04, AB5=>7 0>@B8, 3V?5@B@>DVG=0 >1AB@C:B82=0 :0@4V>?0BVO) 01> ?0FVT=B8 V7
@V4:VA=8< A8=4@<<<

@5?0@0B ?>B5=VNT 3V?>B5=782=89 5D5:B =VB@0BV2 (482. @>74V; «@>B8?>:070==O»
>2V4><;O;>AO ?@> BO6:V ?>1VG=V @50:FVW 7 1>:C A5@F52>-AC48==>W A8AB5<8, 2;:NG0NG8
V=D0@:B :0@40, =5AB01V;L=C AB5=>:0@4VN, @0?B>2C A5@F52C A<5@BL, H;C=>G:>2C 0@8B
20A:C;O@=V :@>2>28;828, B@0=78B>@=C VH5B5=7VN, O:V 70 G0A<< 71V30;8AO V7
70AB>AC20==O< A8;45=0DV;C. # 1V;LH>ABV ?0FVT=BV2, 0;5 =5 C 2AVE, VA=C20;8 D0:B>@8 @878:C
A5@F52>-AC48==8E 70E2>@N20=L. 030B> B0:8E ?>1VG=8E @50:FV9 A?>AB5@V30;>AO ?V4 G0A
01> >4@07C ?VA;O AB0B52>3> 0:BC V ;8H5 :V;L:0 B@0?8;>AO =524>27V ?VA;O 70AB>AC20==O
A8;45=0DV;C 157 A5:AC0;L=>W 0:B82=>ABV. ">

@V0?V70A>18 4;O ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW, C B>15@56=VABN ?0FVT=B0< V7 0=0B>
<0 01> ;59:5

>2V4><;O;>AO ?@> 28?04:8 ?>4>265=>W 5@5:FVW B0 ?@V0?V7 5@5:FVO B@820T 1V;LH =V6 4
3>48=8, ?0FVT=B0< A;V4 =5309=> 725@=CB8AL 70 <548G=>N 4>?><>3>N. 0 2V4ACB=>ABV
=5309=>3> ;V:C20==O ?@V0?V7< <>65 ?@8725AB8 4> ?>H:>465==O B:0=8= ?5=VA0 B0 4> ABV9:>W
2B@0B8 ?>B5=FVW.

4=>G0A=5 70AB>AC20==O 7 V=H8<8 V=3V1VB>@0<8 \$5 01> V=H8<8 ?@5?0@0B0<8 4;O ;V:C20==O
5@5:B8;L=>W 48ADC=:FVW. 57?5:0 B0 5D5:B82=VABL >4=>G0A=>3> 70AB>AC20==O A8;45=0DV;C 7
V=H8<8 V=3V1VB>@0<8 \$5 01> V=H8<8 ?@5?0@0B0<8 4;O ;V:C20==O 3V?5@B5=7VW ;535=52>W
0@B5@VW, O:V AC20==O B0:8E :<<1V=0FV9 =5 @5:<>5=4>20=5.

?;82 =0 7V@. !?>=B0==V ?>2V4><;5==O ?@> 28=8=:5==O 45D5:BV2 7>@C =04E>48;8 0A>FV9>20=> V7
70AB>AC20==O< A8;45=0DV;C B0 V=H8E V=3V1VB>@V2 \$5 (482. @>74V; «>1VG=V @50:FVW»). @>
28?04:8 =50@B5@V0;L=>W ?5@54=L>W VH5W =59@>?0BVW 7>@>2>3> =5@20, I> T @V4:VA=8<
AB0=><, =04E>48;8 A?>=B0==V ?>2V4><;5==O B0 ?>2V4><;O;>AO 0A>FV9>20=> V7 70AB>AC20==O<
A8;45=0DV;C B0 V=H8E V=3V1VB>@V2 \$5 (482. @>74V; «>1VG=V @50:FVW»). 0FVT=BV2 A;V4
?>?5@548B8, I> C @07V @0?B>2>3> ?>@CH5==O 7>@C 70AB>A>2C20==O ?@5?0@0BC A;V4
?@8?8=8B8 B0 =5309=> 725@=CB8AO 4> ;V:0@O (482. @>74V; «@>B8?>:070==O»).

4=>G0A=5 70AB>AC20==O 7 @8B>=02V@>4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0
@8B>=02V@C =5 @5:<>5=4CTBLAO (482. @>74V; «70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0
V=HV 2848 270T<>4V9»).

4=>G0A=5 70AB>AC20==O 7 1;:>.0B>@0<8 α-04@5=>@5F5?B>@V2. 0FVT=B0<, O:V 70AB>A>2CNBL
1;:>.0B>@8 α-04@5=>@5F5?B>@V2, 70AB>A>2C20B8 A8;45=0DV; A;V4 7 >15@56=VABN, >A:V;L:8
B0:0 :<<1V=0FVO <>65 ?@8725AB8 4> A8<0B8G=>W 3V?>B5=7VW C 45O:8E AE8;L=8E 4> FL>3>
?0FVT=BV2. !8<0B8G=0 3V?>B5=7VW 70728G09 28=8:0T ?@>BO3<< 4 3>48= ?VA;O 70AB>AC20==O
A8;45=0DV;C. <5B>N O28 A8@B>AB0B8G=>W 3V?>B5=7VW.

?;82 = 0 :@>2>B5GV. In vitro A8;45=0DV; ?>B5= FVNT 0=B803@530FV9=V 5D5:B8 =0B@VN =VB@>?@CA84C. 5<0T 6>4=>W V=D>@<0FVW I>4> 157?5:8 70AB>AC20==O A8;45=0DV;C ?0FVT=B0 <8 V7 ?>@CH5==O<8 73>@B0==O :@>2V 01> 3>AB@>N ?5?B8G=>N 28@07:>N. "0:8< G8=><, 70AB>AC20==O A8;45=0DV;C ?0FVT=B0<8 FVTW 3@C?8 <>6;825 ;8H5 ?VA;O @5B5;L=>W >FV=:8 A?V22V4=>H5==O :>@8ABV B0 @878:V2.

VA;O 70AB>AC20==O 4>78 100<3 =5 A?>AB5@V30TBLAO 2?;82C =0 <>@D>;>3VN G8 @CE> B@0B0 A;CEC. V:0@O< A;V4 ?>@048B8 ?0FVT=B0< ?@8?8=8B8 70AB>AC20==O V=3V1VB>@V2 \$5, 2;:NG0NG8 A8;45=0DV;; B0 =5309=> 725@=CB8AO 70 <548G=>3> 4>?><3>N C 28?04:0E @0?B>2>3> 7=865==O G8 2B@0B8 A;CEC. @> FV O28I0, O:V B0:>6 <>6CBL AC?@>2>46C20B8AO 472>=>C 2CE0E B0 70?0<>@>G5==O<, ?>2V4><;O;>AO 7 0A>FV0FVTN C G0AV V7 70AB>AC20==O< V=3V1VB>@V2 \$5, 2;:NG0NG8 A8;45=0DV;; . 87=0G8B8, G8 FV O28I0 ?@O<> ?>2O70=V V7 70AB>AC20==O< V=3V1VB>@V2 \$5 G8 7 V=H8<8 D0:B>@0<8 =5<>6;82>.

4=>G0A=5 70AB>AC20==O V7 3V?>B5=782=8<8 ?@5?0@0B0<8. !8;45=0DV;G8=8BL A8AB5<=C AC48=>@>7H8@N20;L=C 4VN B0 <>65 C ?>40;LH>A>2CNBL 3V?>B5=782=V ;V:0@AL:V 70A>18. @8 >4=>G0A=>AC20==V 0<;>48?V=C (5 <3 01>

10 <3) B0 A8;45=0DV;C(100 <3) ?5@>@0;L=> A?>AB5@V30;>AO A5@54=T 4>40B:>25 7=865==O A8AB>;VG=>3> B8A:C =0 8 << @B. AB. B0 4V0AB>;VG=>3> =0 7 << @B. AB.

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

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

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

D5:B8 V=H8E ;V:0@AL:8E 70A>1V2 =0 A8;45=0DV;. 5B01>;V7< A8;45=0DV;C 2V41C20TBLAO ?5@5206=> 70 CG0ABN V7>D>@<8 3□4 (3>;>2=89 H;OE) B0 V7>D>@<8 2!9 (4@C3>@O4=89 H;OE) F8B>E@>

450 (CYP). ">@8 F8E V7>D5@<5=V2 <>6CBL 7=86C20B8 ;;V@5=A A8;45=0DV;C, 0 V=4C:B>@8 F8E V7>D5@<5=V2 <>6CBL ?V428IC20B8 ;;V@5=A A8;45=0DV;C.

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

4=>G0A=5 70AB>AC20==O V=3V1VB>@C -?@>B5078 @8B>=02V@C, 4C65 ?>BC6=>3> V=3V1VB>@0 CYP, C AB0=V @V2=>206=>W :=F5=B@0FVW (500<3 1 @07 =0 4>1C) B0 A8;45=0DV;C (@07>20 4>70 100 <3) ?@872>48;> 4> ?V428I5==O C_{max} A8;45=0DV;C =0 300% (C 4 @078) B0 ?V428I5==O ?;07<>2>W AUC A8;45=0DV;C =0 1000% (2 11 @07V2). '5@57 24 3>48=8 ?;07<>2V @V2=V A8;45=0DV;C 2A5 I5 AB0=>28;8 ?@81;87=> 200 =3/<;, ?>@V2=O=> 7 @V2=5< ?@81;87=> 5 =3/<;, E0@0:B5@=8< 4;O 70AB>AC20==O A8;45=0DV;C >:@5<>, I> 2V4?>2V40T 7=0G=>=02V@C =0 H8@>:89 A?5:B@ AC1AB@0BV2 CYP.

!8;45=0DV; =5 2?;820T =0 D0@<0:>:V=5B8:C @8B>=02V@C. >3;O4C =0 FV D0@<0:>:V=5B8G=V 40=V >4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 @8B>=02V@C =5 @5:>5=4CTBLAO (482. @>74V; «A>1;82>ABV 70AB>AC20==O»); C 1C4L-O:>

4=>G0A=5 70AB>AC20==O V=3V1VB>@0 -?@>B5078 A0:2V=02V@C, V=3V1VB>@0 CYP3A4, C 4>7V, I> 70157?5GCT @V2=>206=C :=F5=B@0FVN (1200 <3 B@8GV =0 4>1C), B0 A8;45=0DV;C (100<3 @07>2>) ?@872>48;> 4> ?V428I5==O C_{max} A8;45=0DV;C =0 140% B0 71V;LH5==O A8AB5<=>W 5:A?>78FVW (AUC) A8;45=0DV;C =0 210%. 5 28O2;5=> 2?;82C A8;45=0DV;C =0 D0@<0:>:V=5B8:C

A0:2V=02V@C (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»). 5@5410G0TBLAO, I> 1V;LH ?>BC6=V V=3V1VB>@8 CYP3A4, B0:V O: :5B>:=>07>; B0 VB@0:=>07>;, 1C4CBL <0B8 1V;LH 28@065=89 2?;82.

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

@59?D@CB>289 AV: T A;01:8 V=3V1VB>@< CYP3A4 C ABV=FV :8H5G=8:C V <>65 28;;8:0B8 ?>2V. 4=>:@0B=5 70AB>AC20==O 0=B0F84V2 (<03=VN 3V4@>:A84C/0;N:A84C) =5 2?;820;> =0 1V>4>ABC?=VABL A8;45=0DV;C.

\$0@<0>:V=5B8:0 A8;45=0DV;C =5 73> >4=>G0A=>AC20==V V7 ;V:0@AL:8<8 70A>10<8, I> =0;560BL 4> 3@C?8 V=3V1VB>@V2 CYP2C9 (B>;1CB0

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

V:>@0=48; O2;OT A>1>N 3V1@84 0:B820B>@0 :0;LFVT28E :0=0;V2 B0 =VB@0BC. VB@0B=89 :=>5=B 7C<>2;NT <>6;82VABL 9>3> A5@9>7=>W 270T<>4VW 7 A8;45=0DV;>

D5:B8 A8;45=0DV;C =0 V=HV ;V:0@AL:V 70A>18.!8;45=0DV; A;01:89 V=3V1VB>@ V7>D>@< 12, 2C9, 2C19, 2D6, 2E1 B0 34 F8B>E@>50 > 150

V4ACB=V 40=V I>4> 270T<>4VW A8;45=0DV;C B0 B0:8E =5A?5F8DVG=8E V=3V1VB>@V2 D>AD>4V5AB5@078, O: B5>DV;V= B0 48?V@840<>;.

A:V;L:8 2V4<>, I> A8;45=0DV;<0T 2?;82 =0 <5B01>;V7<>:A84C 07>BC/F8;;VG=>3> 3C0=>78=<=>D>AD0BC (F\$), 1C;> 2AB0=>2;5=>, I> A8;45=0DV; ?>B5=7VNT 3V?>B5=782=C 4VN =VB@0BV2, B>3> >4=>G0A=5 70AB>AC20==O 7 4>=>@0<8>:A84C 07>BC 01> 7 =VB@0B0<8 C 1C4L-O:V9 D>@ B8?>:070=5 (482. @>74V; «@>B8?>:070==O»).

4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 1;>:0B>@V2 α-04@5=>@5F5?B>@V2 <>65 ?@8725AB8 4> @>728B:C A8<0B8G=>W 3V?>B5=7VW C 450:8E AE8;L=8E 4> FL>3> ?0FVT=V2. "0:0 @50:FVO =09G0ABVH5 28=8:0;0 ?@>B03>< 4 3>48= ?VA;O 70AB>AC20==O A8;45=0DV;C (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78» B0 «A>1;82>ABV 70AB>AC20==O»). @8 70AB>AC20==V 1;>:0B>@0 α-04@5=>@5F5?B>@V2 4>:A07>78=C (4 <3 B0 8 <3) B0 A8;45=0DV;C (25 <3, 50 <3 B0 100 <3) >4=>G0A=> ?0FVT=B0< V7 4>1@>O:VA=>N 3V?5@?;07VTN ?5@54>W 70;>78, AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0 ?@8 70AB>AC20==V 4>:A07>78=C, A?>AB5@V30;>AO A5@54=T 4>40B:>25 7=865==O 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 =0 7/7 << @B. AB., 9/5 << @B. AB. B0 8/4 << @B. AB. B0 A5@54=T 7=865==O 0@B5@V0;L=>3> B8A:C C ?>;>65==V AB>OG8 =0 6/6 << @B. AB., 11/4 << @B. AB., 4/5 << @B. AB. 2V4?>2V4=>. @8 >4=>G0A=>AC20==V A8;45=0DV;C B0 4>:A07>78=C C ?0FVT=V2, AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0 ?@8 70AB>AC20==V 4>:A07>78=C, V=>4V ?>2V4<>;O;>AO ?@> @>728B>: A8<0B8G=>W >@B>AB0B8G=>W 3V?>B5=7VW, 0 A0<5 ?@> 28?04:8 70?0<>@>G5==O B0 AB0= ?5@54 =5?@8B<=VABN, 0;5 157 A8=:>?5

5 A?>AB5@V30;>AO 6>4=8E 7=0GCI8E 270T<>4V9 ?@8 >4=>G0A=>AC20==V A8;45=0DV;C (50<3) V B>;1CB0

!8;45=0DV; (50<3) =5 ?@872>482 4> ?>4>265==O G0AC :@>2>B5GV, A?@8G8=5=>W 70AB>AC20==O< 0F5B8;A0;VF8;>2>W :8A;>B8 (150 <3).

!8;45=0DV; (50<3) =5 ?>B5=7VNT 202 3V?>B5=782=C 4VN 0;>3>;N ?@8 A5@54=VE <0:A8<0;L=8E @V2=OE 5B0=>;C :@>2V 80 <3/4;.

?0FVT=V2, O:V 70AB>A>2C20;8 A8;45=0DV;; =5 A?>AB5@V30;>AO 6>4=8E 2V4AB59 ?@>DV;N ?>1VG=8E 5D5:BV2 ?@8 >4=>G0A=>AC20==V B0:8E ;0AV2 3V?>B5=782=8E ;V:0@AL:8E 70A>1V2, O: 4VC@5B8:8, 1;>:0B>@8 β-04@5=>@5F5?B>@V2, V=3V1VB>@8 \$, 0=B03>=VAB8 0=3V>B5=78=C , 0=B83V?5@B5=782=V ;V:0@AL:V 70A>18 (AC48=>@>7H8@N20;L=V B0 F5=B@0;L=>W 4VW), 1;>:0B>@8 04@5=5@3VG=8E =59@=>V2, 1;>:0B>@8 :0;LFVT28E :0=0;V2 B0 1;>:0B>@8 α-04@5=>@5F5?B>@V2. @8 >4=>G0A=>AC20==V A8;45=0DV;C (100<3) B0 0<;>48?V=C ?0FVT=B0< V7 0@B5@V0;L=>N 3V?5@B5=7VTN A?>AB5@V30;>AO 4>40B:>25 7=865==O A8AB>;VG=>3> 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 =0 8 << @B. AB. V4?>2V4=5 7=865==O 4V0AB>;VG=>3> 0@B5@V0;L=>3> B8A:C AB0=>28;> 7 << @B. AB. 0 25;8G8=>N FV 4>40B:>2V 7=865==O

0@B5@V0;L=>3> B8A:C 1C;8 ?>@V2=O==8<8 V7 B8<8, I> A?>AB5@V30;8AO ?@8 70AB>AC20==V
;8H5 A8;45=0DV;C.
!8;45=0DV; C 4>7V 100 <3 =5 2?;8202 =0 D0@<0>:V=5B8G=V ?>:07=8:8 V=3V1VB>@V2 -?@>B5078,
A0:2V=02V@C B0 @8B>=02V@C, O:V T AC1AB@0B0<8 CYP3A4.
0AB>AC20==O A8;45=0DV;C C @V2=>206=>max 1>A5=B0=C (125 <3 42VGV =0 45=L) =0 49,8 % B0
42 % 2V4?>2V4=>.

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

\$0@<0>;>48=0

5E0=V7< 4VW. !8;45=0DV; T ?@5?0@0B< 4;O ?5@>@0;L=>3> 70AB>AC20==O, ?@87=0G5=8< 4;O
;V:C20==O 5@5:B8;L=>W 48ADC=:FVW. @8 A5:AC0;L=2;NT 7=865=C 5@5:B8;L=C DC=:FVN H;OE<<
?>A8;5==O ?@8B>:C :@>2V 4> ?5=VA0.
\$V7V>;>3VG=89 <5E0=V7<, I> 7C<>2;NT 5@5:FVN, 2;;NG0T 282V;L=5==O >:A84C 07>BC (NO) C
:025@=>7=8E BV;0E ?V4 G0A A5:AC0;L=>3> 71C465==O. 82V;L=5=89 >:A84 07>BC 0:B82CT D5@<5=B
3C0=V;0BF8;;07C, I> AB8> 3C0=>78=<>=>D>AD0BC (F\$), I>, C A2>N G5@3C, 28;;8:0T @>7A;01;5==O
3;04:>W 7=8E BV;, A?@8ONG8 ?@8B>:C :@>2V.
!8;45=0DV; T ?>BC6=8< B0 A5;5:B82=8< V=3V1VB>@<< F\$-A?5F8DVG=>W D>AD>4V5AB5@078 5 (\$5)
C :025@=>7=8E BV;0E, 45 \$5 2V4?>2V40T 70 @>7?04 F\$. D5:B8 A8;45=0DV;C =0 5@5:FVN<0NBL
?5@8D5@8G=89 E0@0:B5@. !8;45=0DV; =5 G8=8BL 157?>A5@54=L>W @5;0:ACNG>W 4VW =0
V7>;L>20=V :025@=>7=V BV;0 ;N48=8, 0;5 ?>BC6=> ?>A8;NT @>7A;01;NNGC 4VN NO =0 40=C
B:0=8=C. @8 0:B820FVW <5B01>;VG=>3> H;OEC NO/F\$, I> 2V41C20TBLAO ?@8 A5:AC0;L=V9 AB8<
\$5 ?@872>48BL 4> ?V428I5==O @V2=O F\$ C :025@=>7=8E BV;0E. "0:8< G8=<<, 4;O B>3>, I>1
A8;45=0DV; 28;;8:02 ?>B@V1=89 D0@<0>;>3VG=89 5D5:B, =5>1EV4=5 A5:AC0;L=5 71C465==O.
?:82 =0 D0@<0>;>48=0 !8;45=0DV; T A5;5:B82=8< 4> \$5, I> 15@5 0:B82=C CG0ABL C ?@>F5AV
5@5:FVW. D5:B A8;45=0DV;C =0 \$5 ?>BC6=VH89, =V6 =0 V=HV 2V4>AD>4V5AB5@078. &59 5D5:B C
10 @07V2 ?>BC6=VH89, =V6 5D5:B =0 \$6, I> 15@5 CG0ABL C ?@>F5A0E D>B>?5@5B2>@5==O C
AVB:V2FV. @8 70AB>AC20==V<0:A8<0;L=8E @5:><5=4>20=8E 4>7 A5;5:B82=VABL A8;45=0DV;C 4>
\$5 C 80 @07V2 ?5@528ICT 9>3> A5;5:B82=VABL 4> \$1, C 700@07V2 28I0, =V6 4> \$2, \$3, \$4, \$7, \$8, \$9,
\$10 B0 \$11. >:@5<0, A5;5:B82=VABL A8;45=0DV;C 4> \$5 C 4000 @07V2 ?5@528ICT 9>3>
A5;5:B82=VABL 4> \$3 F\$-A?5F8DVG=>W V7>D>@<8 D>AD>4V5AB5@078, I> 15@5 CG0ABL C
@53C;OFVW A5@F52>W A:>@>B;82>ABV.

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

1A>@1FVO. !8;45=0DV; H284:> 01A>@1CTBLAO. 0:A8<0;L=V ?;07<>2V :=F5=B@0FVW ?@5?0@0BC
4>AO30NBLAO ?@>BO3<< 30-120 E28;8= (V7 <54V0=>N 60 E28;8=) ?VA;O 9>3> ?5@>@0;L=>3>
70AB>AC20==O =0BI5. !5@54=O 01A>;NB=0 1V>4>ABC?=VABL ?VA;O ?5@>@0;L=>3>
70AB>AC20==O AB0=>28BL 41 % (7 4V0?07>=><< 7=0G5=L 2V4 25 4> 63 %). # @5:><5=4>20=>=V 4>7
(2V4 25 4> 100 <3) ?>:07=8:8 AUC B0 !max A8;45=0DV;C ?VA;O 9>3> ?5@>@0;L=>3> 70AB>AC20==O
?V428ICNBLAO ?@>?>@FV9=> 4> 4>78.
@8 70AB>AC20==V A8;45=0DV;C ?V4 G0A ?@89>@1FVW 7=86CTBLAO V7 A5@54=V< ?>4>265==O< T
max 4> 60 E28;8= V A5@54=V< 7=865==O< Cmax =0 29 %.
>7?>4V;. !5@54=V9 @V2=>206=89 >1T< @>7?>4V;C (Vd) AB0=>28BL 105 ;VB@V2, I> A2V4G8BL ?@>
@>7?>4V; ?@5?0@0BC C B:0=8=0E >@30=V74=>:@0B=>3> ?5@>@0;L=>3> 70AB>AC20==O
A8;45=0DV;C C 4>7V 100 <3 A5@54=O <0:A8<0;L=0 7030;L=0 ?;07<>20 :=F5=B@0FVO A8;45=0DV;C
AB0=>28BL ?@81;87=> 440 =3/<; (:>5DVFT=B 20@V0FVW AB0=>28BL 40%). A:V;L:8 7207C20==O
A8;45=0DV;C B0 9>3> 3>;>2=>3> N-45A<5B8;<-5B01>;VBC 7 1V;;0<8 ?;07<8 4>AO30T 96 %, A5@54=O
<0:A8<0;L=0 ?;07<>20 :=F5=B@0FVO 2V;L=>3> A8;45=0DV;C 4>AO30T 18 =3/<; (38 =<>;L). !BC?V=L
7207C20==O 7 1V;;0<8 ?;07<8 =5 70;568BL 2V4 7030;L=8E :=F5=B@0FV9 A8;45=0DV;C.
>AV1, O:V 70AB>A>2C20;8 A8;45=0DV; >4=>:@0B=> C 4>7V 100<3, G5@57 90 E28;8= 2 50:C;OBV
287=0G0;>AO <5=H5 0,0002 % (C A5@54=L>A>20=>W 4>78.
V>B@0=AD>@<0FVO. 5B01>;V7< A8;45=0DV;C 74V9A=NTBLAO 3>;>2=8< G8=><< 70 CG0ABN A>
<0;L=8E V7>D5@<5=BV2 ?5GV=:8 CYP3A4 (3>;>2=89 H;OE) B0 CYP2C9 (4@C3>@O4=89 H;OE).
>;>2=89 F8@:C;NNG89 <5B01>;VB CB2>@NTBLAO H;OE<< N-45<5B8;N20==O A8;45=0DV;C.
!5;5:B82=VABL <5B01>;VBC 2V4=>A=> \$5 ?>@V2=O==0 7 A5;5:B82=VABN A8;45=0DV;C, 0
0:B82=VABL <5B01>;VBC 2V4=>A=> \$5 AB0=>28BL ?@81;87=> 50 % 0:B82=>ABV 28EV4=>W

@5G>28=8. ;07<>2V :=F5=B@0FVW FL>3> <5B01>;VBC AB0=>2;OBL ?@81;87=> 40 %
:=F5=B@0FVW A8;45=0DV;C C ?;072V. N-45<5B8;L>20=89 <5B01>;VB 707=0T ?>40;LH>3> <5B01>;V7
AB0=>28BL ?@81;87=> 4 3>48=8.

∫ 030;L=89 ∴;V@5=A A8;45=0DV;C AB0=>28BL 41 ;/3>48=C, 7C<>2;NNG8 "½ B@820;VABN
3-5 3>48=. /: ?VA;O ?5@>@0;L=>3>, B0: V ?VA;O 2=CB@VH=L>25==>3> 70AB>AC20==O 5:A:@5FVO
A8;45=0DV;C C 283;O4V <5B01>;VBV2 74V9A=NTBLAO 3>;>2=8< G8=>< V7 :0;>< (?@81;87=> 80 %
22545=>W ?5@>@0;L=>W 4>78) B0 <5=H>N N 7 A5G5N (?@81;87=> 13 % 22545=>W ?5@>@0;L=>W
4>78).

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

0FVT=B8 ;VB=L>3> 2V:C. >AV1 ;VB=L>3> 2V:C (2V:× 2V4 65 @>:V2) 2V47=0G0;>AO 7=865==O
∴;V@5=AC A8;45=0DV;C, I> 7C<>2;N20;> ?V428I5==O ?;07<>28E :=F5=B@0FV9 A8;45=0DV;C B0 9>3>
0:B82=>3> N-45<5B8;L>20=>3> <5B01>;VBC ?@81;87=> =0 90 % ?>@V2=O=> 7 2V4?>2V4=8<8
:=F5=B@0FVO<8 2 >AV1 <>;>4H>3> 2V:C (18-45 @>:V2). # 7207:C V7 2V:>28<8 2V4ABO<8 C
7207C20==V 7 1V;:0<8 ?;07<8 :@>2V 2V4?>2V4=5 ?V428I5==O ?;07<>2>W :=F5=B@0FVW 2V;L=>3>
A8;45=0DV;C AB0=>28;> ?@81;87=> 40%.

8@:>20 =54>AB0B=VABL. >AV1 V7 ?>@CH5==O<8 DC=:FVW =8@>: ;53:>3> B0 ?>3> ABC?5=O
(∴;V@5=A :@50B8=V=C 30-80 <;/E2) D0@<0:>:V=5B8:0 A8;45=0DV;C 70;8H0;0AO =57N ?VA;O 9>3>
>4->:@0B=>3> ?5@>@0;L=>3> 70AB>AC20==O C 4>7V 50 <3. !5@54=V AUC B0 C_{max} N-45
<5B8;L>20=>3> <5B01>;VBC ?V428IC20;8AO =0 126 % B0 73 % 2V4?>2V4=> ?>@V2=O=> 7 B0:8<8
?>:07=8:0<8 2 >AV1 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FVW =8@>: . 4=0: G5@57 28A>:C
V=482V4C0;L=C 20@V015;L=VABL FV 2V4ABV =5 1C;8 AB0B8AB8G=> 7=0GCI8<8. >AV1 V7 B06:8<8
?>@CH5==O<8 DC=:FVW =8@>: (∴;V@5=A :@50B8=V=C =86G5 30 <;/E2) ∴;V@5=A A8;45=0DV;C
7=86C202AO, I> ?@872>48;> 4> A5@54=VE ?V428I5=L AUC B0 C_{max} =0 100 % B0 88 % 2V4?>2V4=>
?>@V2=O=> 7 >A>10<8 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FVW =8@>: . @V< B>3>, 7=0G5==O AUC B0
C_{max} N-45<5B8;L>20=>3> <5B01>;VBC 7=0GCI5 ?V428IC20;8AO =0 79 % B0 200 % 2V4?>2V4=>.

5GV=>20 =54>AB0B=VABL. >AV1 V7 F8@>7× ?5GV=:8 ;53:>3> B0 ?>3> ABC?5=O (∴;0AV2 B0 70
∴;0A8DV:0FVTN '09;40-N) ∴;V@5=A A8;45=0DV;C 7=86C202AO, I> ?@872>48;> 4> ?V428I5==O AUC
(84 %) B0 C_{max} (47 %) ?>@V2=O=> 7 >A>10<8 B0:>3> 6 2V:C 157 ?>@CH5=L DC=:FV9 ?5GV=:8. \$0@
<0:>:V=5B8:0 A8;45=0DV;C C ?0FVT=BV2 V7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 B06:>3> ABC?5=O =5
282G0;0AO.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV: B01;5B:8, 2:@8BV >1>;>=>N, 2V4 1;0:8B=>3> 4> A8=L>3> ∴;L>@C 7 ?5@;028
< 2V4BV=:>< :@C3;>W (4>7C20==O 25 <3, 50 <3 01> 100 <3) 01> @><1>284=>W (4>7C20==O 50 <3 01>
100 <3) D>@<8, 7 42>28?C;>N ?>25@E=5N. >?CA:0TBLAO <0@2VABL 0 ?>25@E=N B01;5B>: @>
<1>284=>W D>@<8 4>?CA:0TBLAO =0=>A8B8 B>20@=89 7=0: ?V4?@8T 7 >4=>3> 1>:C V
4>7C20==O «50» 01> «100» 7 V=H>3>.

"5@ABV. 3 @>:8 (4>7C20==O 25 <3). 5 @>:V2 (4>7C20==O 50 <3 01> 100 <3).

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

15@V30B8 C =54>ABC?=>

#?0:>2:0. "01;5B:8, 2:@8BV >1>;>=>N, ?> 25 <3 1, 1E4 C 1;VAB5@0E C :>@>1FV; ?> 50<3 01> 100 <3 1,
1E2, 1E4, 4 C 1;VAB5@0E C :>@>1FV.

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

8@>1=8:. "«\$0@<0F52B8G=0 :>@>2 O».

VAF57=0E>465==O.#:@0W=0, 61013,