

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

(KONEGRA)

!::04:

4VNG0 @5G>28=0: A8;45=0DV;;

1 B01;5B:0 A8;45=0DV;C 50<3 01> 100 <3;

4>?>28=8: F5;N;>70 :@8AB0;VG=0, =0B@VN :@>A:0@<5;>70, ;0:B>70 <=>3V4@0B,

?>;V2V=V;?V@>;V4>=, :0;LNVN 3V4@>D>AD0B, B0;L:, <03=VN AB50@0B, B8B0=C 4V>:A84 (171),
3V4@>:A8?@>?V;<5B8;F5;N;>70, <0:@>3>; 400, ?>=A> 4R (124).

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV ?;V2:>2>N >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 "!" G0403

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

>:070==O.

V:C20==O ?>@CH5=L 5@5:FVW, I> 287=0G0NBLAO O: =5740B=VABL 4>AO3B8 B0 ?V4B@&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 >=53@8 ?>B@V1=5 A5:AC0;L=5 71C465==O.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> 0:B82=>W @5G>28=8 01> 4> 1C4L-O:>W 7 4>?>28= ?@5?0@0BC.

4=>G0A=5 70AB>AC20==O 7 4>=>@0<8 >:A84C 07>BC (B0:8<8 O: 0 =VB@0B0<8 C 1C4L-O:V9 D>@
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.

'>;>2V:0<, O:8< =5 @5:><5=4>20=0 AB0B520 0:B82=VABL (=0?@8::04 ?0FVT=B8 7 BO6:8<8 A5@F52>-
AC48==8<8 @>7;040<8, B0:8<8 O: =5AB01V;L=0 AB5=>:0@4VO B0 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 =59@>?0BVW 7>@>2>3>
=5@20, =570;56=> 2V4 B>3>, G8 ?>2O70=0 FO ?0B>;>3VO V7 ?>?5@54=V< 70AB>AC20==O<
V=3V1VB>@V2 \$5.

>@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 <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?5G=VABL A8;45=0DV;C =5
4>A;V46C20;0AO C B0:8E ?V43@C? ?0FVT=V2.

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

"01;5B:8 ?@87=0G5=V 4;O ?5@>@0;L=>3> ?@89>1EV4=5 AB0B525 71C465==O.

5:><5=4>20=0 4>70 >=53@8 AB0=>28BL 50<3 B0 70AB>A>2CTBLAO, ?@8 =5>1EV4=>ABV, ?@81;87=>
70 1 3>48=C 4> AB0B52>3> 0:BC. 0;56=> 2V4 5D5:B82=>ABV B0 ?5@5=>A8<>ABV ?@5?0@0BC 4>7C
<>6=0 71V;LH8B8 4> 100 <3 01> 7<5=H8B8 4> 25 <3. 0:A8<0;L=0 @5:><5=4>20=0 4>70 AB0=>28BL
100 <3.

0:A8<0;L=0 @5:><5=4>20=0 G0AB>B0 70AB>AC20==O ?@5?0@0BC AB0=>28BL 1 @07 =0 4>1C. @8
70AB>AC20==V ?@5?0@0BC >=53@0 ?V4 G0A ?@89>

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

5>1EV4=VABL C :>@5:FVW 4>78 4;O ?0FVT=V2 ;VB=L>3> 2V:C 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 2V4 30 4> 80 <;/E2) @5:>5=4>20=0 4>70 ?@5?0@0BC T 0=0;>3VG=>N 4>7V, =02545=V9
28I5.

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
=86G5 30 <;/E2) ;V@5=A A8;45=0DV;C 7=865=89, @5:>5=4>20=0 4>70 ?@5?0@0BC AB0=>28BL 25 <3.
0;56=> 2V4 5D5:B82=>ABV B0 ?5@5=>A8<>ABV ?@5?0@0BC 4>7C <>6=0 71V;LH8B8 4> 50 <3 B0 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, @5:>5=4>20=0 4>70 ?@5?0@0BC AB0=>28BL 25 <3. 0;56=> 2V4 5D5:B82=>ABV B0
?5@5=>A8<>ABV ?@5?0@0BC 4>7C <>6=0 71V;LH8B8 4> 50 <3 B0 100 <3.

0FVT=B8, O:V 70AB>A>2CNBL V=HV ;V:0@AL:V 70A>18.

5:>5=4>20=0 ?>G0B:>20 4>70 ?@5?0@0BC ?0FVT=B0<, O:V 70AB>A>2CNBL V=3V1VB>@8 CYP3A4
70 28=OB:>< @8B>=02V@C, AB0=>28BL 25 <3.

<5B>N 728B:C >@B>AB0B8G=>W 3V?>B5=7VW AB0= ?0FVT=BV2, O:V 70AB>A>2CNBL 1;>:0B>@8
0;LD0-04@5=>@5F5?B>@V2, <0T 1CB8 AB01V;V7>20=89 4> ?>G0B:C 70AB>A>2C20==O A8;45=0DV;C.
"0:>6 @5:>5=4>20=0 ?>G0B:>20 4>70 A8;45=0DV;C AB0=>28BL 25 <3.

@5?0@0B >=53@0 =5 ?@87=0G5=89 4;O 70AB>AC20==O 6V=:0<.

>1VG=V @50:FVW.

09G0ABVH5 <>6;82V B0:V ?>1VG=V @50:FVW O: 3>;>2=89 1V;L, ?@8?;828, 48A?5?AVO, @>7;048
7>@C, 70::045=VABL =>A0, 70?0<>@>G5==O B0 ?>@CH5==O A?@89=OBBO :>;L>@V2.

>7;048 7 1>:C VW A8AB5<8: @50:FVW 3V?5@GCB;82>ABV.

>7;048 7 1>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O, A>=:82VABL, 3V?5AB57VO,
V=AC;LB, =5?@8B><=VABL, B@0=78B>@=0 VH5<8, @5F84828 AC4>

>7;048 7 1>:C >@30=V2 7>@C: @>7;048 7>@C, 70BC<0=5==O 7>@C, ?>@CH5==O A?@89=OBBO
:>;L>@C, A2VB;0, @>7;048 7 1>:C :>=N=:B828, @>7;048 A;L>7>284V;5==O, V=HV @>7;048 7 1>:C

>@30=V2 7>@C, =50@B5@V0;L=0 ?5@54=O VH5?0BVO 7>@>2>3> =5@20, >;N7VO AC48= AVB:V2:8,
45D5:B8 ?>;O 7>@C.

>7;048 7 1>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC: 70?0<>@>G5==O, HC< C 2CE0E,
3;CE>B0 (?@8 70AB>AC20==V 2AVE V=3V1VB>@V2 \$5, 2::NG0NG8 A8;45=0DV;; ?>2V4<;O;>AO ?@>

=525;8:C :V;L:VABL 28?04:V2 @0?B>2>3> 7=865==O 01> 2B@0B8 A;CEC).

>7;048 7 1>:C AC48=: ?@8?;828, 3V?5@B5=7VO, 3V?>B5=7VO.

>7;048 7 1>:C A5@FO: ?>A8;5=5 A5@F518BBO, B0EV:0@4VO, V=D0@:B:0@40, DV1@8;OFVO
?5@54A5@4L, H;C=>G:>20 0@8B:0@4VO, @0?B>20 A5@F520 A<5@BL.

>7;048 7 1>: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.

>7;048 7 1>:C H;C=:>2>-.8H:>2>3> B@0:BC: 48A?5?AVO, =C4>B0, 1;N20==O, ACEVABL C @>BV.

>7;048 7 1>:C H:V@8 B0 ?V4H:V@=>W B:0=8=8: 28A8?0==O =0 H:V@V, A8=4@< !BV25=A0-
6=>A>=0, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7.

>7;048 7 1>:C >?>@=>-@CE>2>3> 0?0@0BC B0 A?>;CG=>W B:0=8=8:.

>7;048 7 1>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: ?@V0?V7<, ?>4>265=0 5@5:FVO.
030;L=V @>7;048 B0 @50:FVW C 1V;L C 3@C4OE, ?V428I5=0 AB<;N20=VABL.

1AB565==O: ?V428I5=0 G0AB>B0 A5@F528E A:>@>G5=L

5@54>7C20==O.

@8 70AB>AC20==V @07>2>W 4>78 A8;45=0DV;C 4> 800<3 ?>1VG=V @50:FVW ?>4V1=V 4> B8E, I>
A?>AB5@V30NBLAO ?@8 70AB>AC20==V A8;45=0DV;C C =86G8E 4>70E, 0;5 7CAB@VG0NBLAO

G0ABVH5 B0 1V;LH BO6:V. 0AB>A>2C20==O A8;45=0DV;C C 4>7V 200<3 =5 ?@872>48BL 4>
?V428I5==O 5D5:B82=>ABV, 0;5 A?@8G8=OT 7@>AB0==O :V;L:>ABV 28?04:V2 @>728B:C ?>1VG=8E

@50:FV9 (3>;>2=>3> 1>;N, ?@8?;82V2, 70?0<>@>G5==O, 48A?5?AVW, 70::045=>ABV =>A0, ?>@CH5=L
7 1>:C >@30=V2 7>@C).

28?04:C ?5@54>7C20==O ?@8 =5>1EV4=>ABV 240NBLAO 4> A8<0B8G=>W B5@0?VW.

@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 2 ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

@5?0@0B >=53@0 =5 ?@87=0G5=89 4;O 70AB>AC20==O 6V=:0<.

VB8.

@5?0@0B >=53@0 =5 ?>:070=89 4;O 70AB>AC20==O 4VBO<.

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=
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;<0T AC48=>@>7H8@N20;L=89 5D5:B, 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 G8=8B8 =5A?@8OB;8289 2?;82 =0 ?0FVT=BV2 V7 ?52=8<8
>A=>2=8<8 70E2>@N20==O<8, >A>1;82> C :><1V=0FVW 7V AB0B52>N 0:B82=VABN. > ?0FVT=BV2
V7 ?V428I5=>N GCB;82VABN 4> 207>48;0B0B>@V2 =0;560BL ?0FVT=B8 7 >1AB@C:FVTN 282V4=>3>
B@0:BC ;V2>3> H;C=>G:0 (=0?@8;:04 AB5=>7 0>@B8, 3V?5@B@>DVG=0 >1AB@C:B82=0 :0@4V>
?0BVO), 01> ?0FVT=B8 7 @V4:VA=8< A8=4@>>><

!8;45=0DV; ?>B5=VFN 3V?>B5=782=89 5D5:B =VB@0BV2.

>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 7 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. ">

0A>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

57?5G=VABL B0 5D5:B82=VABL >4=>G0A=>3> 70AB>AC20==O A8;45=0DV;C 7 V=H88 <5B>40<8
;V:C20==O 5@5:B8;L=>W 48ADC=:FVW =5 282G0;8AO, B>AC20==O B0:8E :><1V=0FV9 =5 @5:>
<5=4CTBLAO.

>2V4><;O;>AO ?@> @>7;048 7>@C B0 28?04:8 =50@B5@V0;L=>W ?5@54=L>W VH5W =59@>?0BVW
7>@>2>3> =5@20, ?>2O70=V V7 70AB>AC20==O< A8;45=0DV;C B0 V=H8E V=3V1VB>@V2 \$5.
0FVT=BV2 A;V4 ?>?5@548B8, I> C 28?04:C @0?B>2>3> ?>@CH5==O 7>@C 70AB>A>2C20==O
?@5?0@0BC >=53@0 A;V4 ?@8?8=8B8 B0 =5309=> 725@=CB8AO 4> ;V:0@O.

4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 @8B>=02V@C =5 @5:><5=4CTBLAO.

0FVT=B0<, O:V 70AB>A>2CNBL 1;>:0B>@8 0;LD0-04@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=7VO 70728G09 28=8:0T
?@>BO3>< 4 3>48= ?VA;O 70AB>AC20==O A8;45=0DV;C.<5B>N 728B:C >@B>AB0B8G=>W
3V?>B5=7VW B5@0?VN A8;45=0DV;>< <>6=0 @>7?>G8=0B8 ;8H5 C 35<>48=0 AB01V;L=8E
?0FVT=BV2, O:V 70AB>A>2CNBL 1;>:0B>@8 0;LD0-04@5=>@5F5?B>@V2. 5:><5=4>20=0 ?>G0B:>20
4>70 B0:8< ?0FVT=B0< AB0=>28BL 25<3 A8;45=0DV;C. @V< B>3>, A;V4 ?@>V=D>@O28 A8
@B>AB0B8G=>W 3V?>B5=7VW.

>A;V465==O B@><1>F8BV2 ;N48=8 ?@>45<=>AB@C20;8, I> *in vitro* A8;45=0DV; ?>B5=VFN
0=B803@530FV9=V 5D5:B8 =0B@VN =VB@>?@CA84C. 5<0T 6>4=>W V=D>@<0FVW I>4>
157?5G=>ABV 70AB>AC20==O A8;45=0DV;C ?0FVT=B0< V7 ?>@CH5==O<8 73>@B0==O :@>2V 01>
3>AB@>N ?5?B8G=>N 28@07:>N. "0:8< G8=><, 70AB>AC20==O A8;45=0DV;C ?0FVT=B0< FVTW
3@C?8 <>6;825 ;8H5 ?VA;O @5B5;L=>W >FV=:8 A?V22V4=>H5==O :>@8ABV B0 @878:V2.
@5?0@0B >=53@0 7C, =5 A;V4 70AB>A>2C20B8 G>;>2V:0< V7 B0:8<8 @V4:VA=8<8 A?04:>28<8
?>@CH5==O<8 O: =5?5@5=>A878, =54>AB0B=VABL ;0:B078 0??0 01>
<0;L01A>@1FVO 3;N:>78-30;0:B>78.

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 <5E0=V7<0<8 =5 ?@>2>48;>AO.

A:V;L:8 ?@8 70AB>AC20==V A8;45=0DV;C<>6;82V 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=> 7OAC20B8, O:>N T WE=O V=482V4C0;L=0 @50:FVO =0
70AB>AC20==O ?@5?0@0BC >=53@0.

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;.

>A;V465==O *in vitro*.

5B01>;V7< A8;45=0DV;C 2V41C20TBLAO ?5@5206=> 70 CG0ABV V7>D>@<8 34 (3>;>2=89 H;OE) B0
V7>D>@<8 2!9 (4@C3>@O4=89 H;OE) F8B>E@>@8 F8E V7>D5@<5=BV2 740B=V 7=86C20B8 ;;V@5=A
A8;45=0DV;C.

>A;V465==O *in vivo*.

V47=0G0TBLAO 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, @5:<>5=4>20=0 ?>G0B:>20 4>70
A8;45=0DV;C AB0=>28BL 25<3.

4=>G0A=5 70AB>AC20==O V=3V1VB>@0 -?@>B5078 @8B>=02V@C, 4C65 ?>BC6=>3> V=3V1VB>@0
450, C AB0=V @V2=>206=>W :=F5=B@0FVW (500<3 1 @07 =0 4>1C) B0 A8;45=0DV;C (@07>20 4>70
100 <3), ?@872>48;> 4> ?V428I5==O C_{max} A8;45=0DV;C =0 300 % (C 4 @078) B0 ?V428I5==O ?;07<>2>W
AUC A8;45=0DV;C =0 1000 % (C 11 @07V2). '5@57 243>48=8 ?;07<>2V @V2=V A8;45=0DV;C 2A5 I5
AB0=>28;8 ?@81;87=> 200 =3/<; ?>@V2=O=> 7 @V2=5< ?@81;87=> 5 =3/<;, E0@0:B5@=8< 4;O
70AB>AC20==O A8;45=0DV;C >:@5<>, I> 2V4?>2V40T 7=0G=>=02V@C =0 H8@>:89 A?5:B@
AC1AB@0BV2 450. !8;45=0DV; =5 2?;820T =0 D0@<0>:V=5B8:C @8B>=02V@C. >3;O4C =0 FV D0@
<0>:V=5B8G=V 40=V >4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 @8B>=02V@C =5 @5:>
<5=4CTBLAO; 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. 5@5410G0TBLAO, I> 1V;LH ?>BC6=V V=3V1VB>@8 CYP3A4, B0:V O: :5B>:=>07>; B0
VB@0:=>07>;, 1C4CBL <0B8 1V;LH 28@065=89 2?;82.

@8 70AB>AC20==V A8;45=0DV;C (100<3 @07>2>) B0 5@8B@>3> V=3V1VB>@C CYP3A4, C
@V2=>206=>UC). # 74>@>28E 4>1@>2>;LFV2 G>;>2VG>W AB0BV =5 A?>AB5@V30;>AO 2?;82C
078B@>max, T_{max}: :=AB0=BC H284:>ABV 5;V40;LH89 ?5@V>4 =0?V2282545==O A8;45=0DV;C 01>
9>3> 3>;>2=>3> F8@:C;NNG>3> <5B01>;VBC. &8<5B848= (V=3V1VB>@ F8B>E@>@ CYP3A4) C 4>7V
800 <3 ?@8 >4=>G0A=>AC20==V V7 A8;45=0DV;C < C 4>7V 50 <3 C 74>@>28E 4>1@>2>;LFV2
?@872>482 4> ?V428I5==O ?;07<>28E :=F5=B@0FV9 A8;45=0DV;C =0 56%.

@59?D@CB>289 AV: T A;01:8 V=3V1VB>@< CYP3A4 C ABV=FV :8H5G=8:C V<>65 28;;8:0B8 ?>
4=>:@0B=5 70AB>AC20==O 0=B0F84=8E 70A>1V2 (<03=VN 3V4@>:A84C/0;N:A84C) =5 2?;820T =0
1V>4>ABC?=VABL A8;45=0DV;C.

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

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;C>

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

>A;V465==O *in vitro*

!8;45=0DV; A;01:89 V=3V1VB>@ V7>D>@< 12, 2C9, 2C19, 2D6, 2E1 B0 34 (□ 50 > 150 2V ?;07<>2V
:=F5=B@0FVW A8;45=0DV;C AB0=>2;OBL ?@81;87=>

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

>A;V465==O *in vivo*.

A;V;L:8 2V4<>, I> A8;45=0DV;<0T ??:82 =0 <5B01>;V7< >:A84C 07>BC/F8;;VG=>3> 3C0=>78= <=>D>AD0BC (F\$), 1C;> 2AB0=>2;5=>, I> F59 ?@5?0@0B ?>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 2 1C4L-O:V9 D>@B8?>:070=5.

450:8E AE8;L=8E 4> FL>3> ?0FVT=BV2 >4=>G0A=5 70AB>AC20==O A8;45=0DV;C B0 1;>:0B>@V2 0;LD0-04@5=>@5F5?B>@V2 <65 ?@8725AB8 4> @>728B:C A8<0B8G=>W 3V?>B5=7VW, I> =09G0ABVH5 28=8:0;0 ?@>BO3<< 4 3>48= ?VA;O 70AB>AC20==O A8;45=0DV;C. # E>4V 4>A;V465=L A?5F8DVG=>W 270T<>4VW ;V:0@AL:8E 70A>1V2 1;>:0B>@ 0;LD0-04@5=>@5F5?B>@V2 4>:A07>78= (4 <3 B0 8 <3), B0 A8;45=0DV; (25 <3, 50 <3 B0 100 <3) 70AB>A>2C20;8 >4=>G0A=> ?0FVT=B0< V7 4>1@>O:VA=>N 3V?5@?;07VTN ?5@542>W 70;>78 (), AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0 ?@8 70AB>AC20==V 4>:A07>78=C. # F8E 4>A;V46C20=8E ?>?C;OFVOE A?>AB5@V30;>AO A5@54=T 4>40B:>25 7=865==O 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 =0 7/7 <3> B8A:C C ?>;>65==V AB>OG8 =0 6/6 <2V4=>. @8 >4=>G0A=>AC20==V A8;45=0DV;C B0 4>:A07>78=C C ?0FVT=BV2, AB01V;V70FVO AB0=C O:8E 1C;0 4>AO3=CB0 ?@8 70AB>AC20==V 4>:A07>78=C, V=>4V ?>2V4> <;O;>AO ?@> @>728B>: A8<0B8G=>W >@B>AB0B8G=>W 3V?>B5=7VW. # F8E ?>2V4<;5==OE 9H;>AO ?@> 28?04:8 70?0<>@>G5==O B0 ?5@54=5?@8B<=<89 AB0=, 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=782=C 4VN 0;>3>;N 74>@>28E 4>1@>2>;LFV2 ?@8 A5@54=VE <0:A8<0;L=8E @V2=OE 5B0=>;C :@>2V 80 <3/4;.

?0FVT=BV2, O:V 70AB>A>2C20;8 A8;45=0DV;; =5 A?>AB5@V30;>AO 6>4=8E 2V4AB59 ?@>DV;N ?>1VG=8E 5D5:BV2 ?>@V2=O=> ? ?;0F51> ?@8 >4=>G0A=>AC20==V B0:8E ;0AV2 3V?>B5=782=8E ;V:0@AL:8E 70A>1V2 O: 4VC@5B8:8, 1;>:0B>@8 15B0-04@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 0;LD0-04@5=>@5F5?B>@V2. # A?5FV0;L=>A;V465==V 270T<>4VW ?@8 >4=>G0A=> AC20==V A8;45=0DV;C (100<3) B0 0<;>48?V=C ?0FVT=B0< 7 0@B5@V0;L=>N 3V?5@B5=7VTN A?>AB5@V30;>AO 4>40B:>25 7=865==O A8AB>;VG=>3> 0@B5@V0;L=>3> B8A:C 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 A?V2AB02=8<8 7 B8<8, I> A?>AB5@V30;8AO ?@8 70AB>AC20==V ;8H5 A8;45=0DV;C C 74>@>28E 4>1@>2>;LFV2.

!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.

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

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

!8;45=0DV; T ?@5?0@0B< 4;O ?5@>@0;L=>3> 70AB>AC20==O, ?@87=0G5=89 4;O ;V:C20==O 5@5:B8;L=>W 48ADC=:FVW. @8 AB0B52V9 AB&;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 AB0B52>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;045=L:>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 =>AOBL ?5@8D5@8G=89 E0@0:B5@. !8;45=0DV; =5 A?@8G8=OT 157?>A5@54=L>W @5;0:ACNG>W 4VW =0 V7>;L>20=V :025@=>7=V BV;0 ;N48=8, 0;5 ?>BC6=> ?>A8;NT @>7A;01;NNGC 4VN NO =0 40=C B:0=8=C. @8 0:B820FVW <5B01>;VG=>3> H;OEC NO/F\$, I> 2V41C20TBLAO ?@8 AB0B52V9 AB8< \$5 ?@872>48BL 4> ?V428I5==O @V2=O F\$ C :025@=>7=8E BV;0E. "0:8< G8=><, 4;O B>3>, I>1 A8;45=0DV; 28;;8:02 =5>1EV4=89 D0@<0>;>3VG=89 5D5:B, =5>1EV4=5 AB0B525 71C465==O.

>A;V465==O in vitro A8;45=0DV;C ?>:070;8 A5;5:B82=VABL 2?;82C A8;45=0DV;C =0 \$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 @07 ?>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.

:;V=VG=8E 4>A;V465==OE A8;45=0DV;C 70 CG0ABN ?0FVT=BV2, O:V 70AB>A>2C20;8 A8;45=0DV; =0BI5, ?@8 ?@>2545==V D0;;>?;5B87<3@0DVW (RigiScan) <54V0=0 G0AC 4> ?>G0B:C 5@5:FVW C ?0FVT=BV2, O:V 4>AO3;8 5@5:FVW V7 @83V4=VABN 60 % (4>AB0B=L>N 4;O 74V9A=5==O AB0B52>3> :>=B0:BC), AB0=>28;0 25 E28;8= (C 4V0?07>=V 7=0G5=L 12-37 E28;8=). >:@5<>A;V465==V V7 28:>@8AB0==O< RigiScan A8;45=0DV; 2A5 I5 1C2 740B=89 28;;8:0B8 5@5:FVN G5@57 4-5 3>48= ?VA;O 70AB>AC20==O.

!8;45=0DV; A?@8G8=OT ;53:5 B0 :>@>B:>G0A=5 7=865==O 0@B5@V0;L=>3> B8A:C, I> C 1V;LH>ABV 28?04:V2 =5 <0T ;;V=VG=8E ?@>O2V2. !5@54=T <0:A8<0;L=5 7=865==O A8AB>;VG=>3> 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 ?VA;O ?5@>@0;L=>3> 70AB>AC20==O A8;45=0DV;C C 4>7V 100 <3 AB0=>28;> 8,4 <<. @B.AB. V4?>2V4=0 7;VG=>3> 0@B5@V0;L=>3> B8A:C C ?>;>65==V ;560G8 AB0=>28;0 5,5 <<. @B.AB. &V 7=865==O 0@B5@V0;L=>3> B8A:C 4>1@5 C73>46CNBLAO V7 AC48=>@>7H8@N20;L=>N 4VTN A8;45=0DV;C, <>6;82>, 2=0A;V4>: ?V428I5==O @V2=V2 F\$ C 3;045=L:V9 :@0B=5 ?5@>@0;L=5 70AB>AC20==O A8;45=0DV;C 2 4>70E 4> 100 <3 C 74>@>28E 4>1@>2>;Lfv2 =5 28;;8:0;> 6>4=8E ;;V=VG=> 7=0GCI8E 7:0@4V>3@0

4>A;V465==V 35<>48=04=>:@0B=>3> ?5@>@0;L=>3> 70AB>AC20==O A8;45=0DV;C C 4>7V 100<3 C 14 ?0FVT=BV2 V7 BO6:>N VH5N E2>@>1>N A5@FO (%) (7V AB5=>7< I=>09<5=H5 >4=VTW :>@>=0@=>W 0@B5@VW 1V;LH =V6 70 %), A5@54=V9 A8AB>;VG=89 B0 4V0AB>;VG=89 0@B5@V0;L=89 B8A: C AB0=V A?>:>N 7=86C202AO =0 7 % B0 6 % 2V4?>2V4=> 2V4=>A=> ?>G0B:>2>3> @V2=O. !5@54=V9 ;535=5289 A8AB>;VG=89 B8A: 7=86C202AO =0 9 %. !8;45=0DV; =5 ?@872>482 4> 7:07=8:V2 A5@F52>3> 28:84C B0 =5 7<5=HC202 :@>2>B>: ?> AB5=>7>20=8E :>@>=0@=8E 0@B5@VOE.

>4=8E ;;V=VG=> 7=0GCI8E 2V4AB59 =5 1C;> ?@>45<>=AB@>20=> 4;O G0AC 4> 28=8:=5==O ;VW AB5=>:0@4VW ?@8 70AB>AC20==V A8;45=0DV;C ?>@V2=O=> 7 ?;0F51> C ?>42V9=>-A;V?8E ?;0F51>:->=B@>;L>20=8E ;;V=VG=8E 4>A;V465==OE V7 28:>@8AB0==O< B5ABC 7 DV78G=8< =020=B065==O< 70 CG0ABN 144 ?0FVT=BV2 7 5@5:B8;L=>N 48ADC=:FVTN B0 E@>=VG=>N AB01V;L=>N AB5=>:0@4VTN, O:V ?>ABV9=> 70AB>A>2C20;8 0=B80=3V=0;L=V ;V:0@AL:V 70A>18 (:@V< =VB@0BV2).

53:V B0 B82V ?>@CH5==O 740B=>ABV @>7@V7=OB8 :>;L>@8 (1;0:8B=89/75;5=89) 1C;8 28O2;5=V C 45O:8E ?0FVT=BV2 ?@8 ?@>2545==V 100-2V4BV=:>2>3> B5ABC \$0@=A2>@B0=0=A5;;0 G5@57 1 3>48=C ?VA;O 70AB>AC20==O A8;45=0DV;C C 4>7V 100<3. &V 5D5:B8 ?>2=VABN 7=8:0;8 G5@57 2 3>48=8 ?VA;O 70AB>AC20==O ?@5?0@0BC. >6;8289 <5E0=V7< FVTW 77?V7=020==V :>;L>@V2 ?>2O70=89 7 V=3V1C20==O< \$6, I> 15@5 CG0ABL C D>B>?5@5B2>@N20;L=>AB@>BC 7>@C 01> :>=B@0AB=C GCB;82VABL. # =525;8:8E ?;0F51>:->=B@>;L>20=8E ;;V=VG=8E 4>A;V465==OE 70 CG0ABN ?0FVT=BV2 V7 4>:C<5=B0;L=> ?V4B25@465=>N <0:C;O@=>N 48AB@>DVTN (n=9), 70AB>AC20==O A8;45=0DV;C (>4=>:@0B=>, C 4>7V 100<3) =5 28;;8:0;> 4>AB>2V@=8E 72545=8E 4>A;V465=L 7>@C (3>AB@>B0 7>@C, AVB:0B>AB@5A).

4=>:@0B=5 ?5@>@0;L=5 70AB>AC20==O A8;45=0DV;C C 4>7V 100<3 74>@>28<8 4>1@>2>;LFO<8 =5 2?;820;> =0 @CE;82VABL 01><>@D>;>3VN A?5@<0B>7>W4V2.

>40B:>2V 40=V ;;V=VG=8E 4>A;V465=L.

:;V=VG=8E 4>A;V465==OE A8;45=0DV; 70AB>A>2C20;8 1V;LH =V6 8000 ?0FVT=B0< 2V:< 2V4 19 4> 87 @>:V2. C;8 ?@54AB02;5=V =0ABC?>V 3@C?8 ?0FVT=BV2: ?0FVT=B8 ;VB=L>3> 2V:C (19,9 %), ?0FVT=B8 7 0@B5@V0;L=>N 3V?5@B5=7VTN (30,9 %), ?0FVT=B8 7 FC:@>28< 4V015B<< (20,3 %), VH5N E2>@>1>N A5@FO (5,8 %), 3V?5@;V?V452>W 70;>78 (3,7 %), @048:0;L=>N ?@>AB0B5:B> AB0B=L>N N 01> =5 2;;NG0;8AO 4> ;;V=VG=8E 4>A;V465=L: ?0FVT=B8 ?VA;O EV@C@3VG=>3> 2B@CG0==O =0 >@30=0E B070, ?0FVT=B8 ?VA;O ?@><5=52>W B5@0?VW, ?0FVT=B8 V7 BO6:>N =8@:>2>N 01> ?5GV=:>2>N =54>AB0B=VABN B0 ?0FVT=B8 7 45O:8<8 A5@F52>-AC48==8<8 70E2>@N20==O<8.

4>A;V465==OE 70AB>AC20==O DV:A>20=>W 4>78 :V;L:VABL ?0FVT=BV2, O:V ?>2V4<;O;8 ?@> ?>:@0I5==O 5@5:B8;L=>W DC=:FVW, AB0=>28;0 62 % (25<3), 74 % (50<3), B0 82 % (100<3) ?>@V2=O=> 7 25 % C 3@C?V ?;0F51>. # :>=B@>;L>20=8E ;;V=VG=8E 4>A;V465==OE :V;L:VABL 28?04:V2 2V4N B0 ?>4V1=>N 4> B0:>W C 3@C?V ?;0F51>. ;O CAVE F8E 4>A;V465=L :V;L:VABL ?0FVT=BV2, O:V ?>2V4<;O;8 ?@> ?>:@0I5==O ?@8 70AB>AC20==V A8;45=0DV;C, 1C;0 =0ABC?=>N: ?A8E>35==0 5@5:B8;L=0 48ADC=:FVO (84 %), 7 @30=VG=0 5@5:B8;L=0 48ADC=:FVO (68 %), ?0FVT=B8 ;VB=L>3> 2V:C (67 %), FC:@>289 4V015B (59 %), VH5@>10 A5@FO (69 %), 3V?5@B5=7VO (68 %), B@0=AC@5B@0;L=0 @575:FVO ?5@542>W 70;>78 (61 %), @048:0;L=0 ?@>AB0B5:B> 40=8<8 4>23>AB@>:>28E 4>A;V465=L. \$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< C_{max} =0 29 %. >7?>4V; !5@54=V9 @V2=>206=89 >1T< @>7?>4V;C (V_d) 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/<; (:>5DVVVT=B 20@V0FVW AB0=>28BL 40 %). A:V;L:8 72O7C20==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?5=L 72O7C20==O 7 1V;;0<8 ?;07<8 =5 70;568BL 2V4 7030;L=8E :=F5=B@0FV9 A8;45=0DV;C. # 74>@>28E 4>1@>2>;LFBV2, O:V 70AB>A>2C20;8 A8;45=0DV; >4=>:@0B=> C 4>7V 100<3, G5@57 90 E28;8= 2 5O:C;OBV 287=0G0;>AO <5=H5 0,0002 % (2 A5@54=L>A>20=>W 4>78. 5B01>;V7 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=>H5==N 4> \$5 A?V2AB02=0 7 A5;5:B82=VABN A8;45=0DV;C, 0 0:B82=VABL<5B01>;VBC ?> 2V4=>H5==N 4> \$5 AB0=>28BL ?@81;87=> 50 % 2V4 0:B82=>ABV ?>G0B:>2>W @5G>28=8. ;07<>2V :=F5=B@0FVW FL>3> <5B01>;VBC AB0=>2;OBL ?@81;87=> 40 % 2V4 :=F5=B@0FV9 A8;45=0DV;C C ?;072V. N-45<5B8;L>20=89 <5B01>;VB 707=0T ?>40;LH>3> <5B01>;V74 9>3> =0?V2282545==O AB0=>28BL ?@81;87=> 4 3>48=8. ;V 030;L=89 ;;V@5=A A8;45=0DV;C AB0=>28BL 41 ;/3>4, 7C>2;NNG8 ?5@V>4 9>3> =0?V2282545==O B@820;VABN 3-5 3>48=. /: ?VA;O ?5@>@0;L=>3>, B0: V ?VA;O 2=CB@VH=L>25==>3> 70AB>AC20==O 5:A:@5FVO A8;45=0DV;C C 283;O4V<5B01>;VVBV2 74V9A=NTBLAO 3>;>2=8< G8=>< V7 :0;>< (?@81;87=> 80 % 2V4 22545=>W ?5@>@0;L=>W 4>78) B0, <5=H>N N, 7 A5G5N (?@81;87=> 13 % 2V4 22545=>W ?5@>@0;L=>W 4>78). 0FVT=B8 ;VB=L>3> 2V:C. # 74>@>28E 4>1@>2>;LFBV2 ;VB=L>3> 2V:C (2V:> 65 @>:V2 B0 AB0@H5) 2V47=0G0;>AO 7=865==O ;V@5=AC A8;45=0DV;C, I> 7C>2;N20;> ?V428I5==O ?;07<>28E :=F5=B@0FV9 A8;45=0DV;C B0 9>3> 0:B82=>3> N-45<5B8;L>20=>3> <5B01>;VBC ?@81;87=> =0 90 % ?>@V2=O=> 7 2V4?>2V4=8<8 :=F5=B@0FVO<8 C 74>@>28E 4>1@>2>;LFBV2 <>;>4H>3> 2V:C (18-45 @>:V2). # 72O7:C 7 2V:>28<8 2V4ABO<8 C 72O7C20==V 7 1V;;0<8 ?;07<8 :@>2V 2V4?>2V4=5 ?V428I5==O ?;07<>2>W :=F5=B@0FVW 2V;L=>3> A8;45=0DV;C AB0=>28;> ?@81;87=> 40 %. 8@:>20 =54>AB0B=VABL. # 4>1@>2>;LFBV2 V7 ?>@CH5==O<8 DC=:FVW =8@>: ;53>3> B0 ?>3> ABC?5=O B06:>ABV (:;V@5=A :@50B8=V=C 2V4 30 4> 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 C 4>1@>2>;LFBV2 0=0;>3VG=>3> 2V:C 157 ?>@CH5=L DC=:FVW =8@>:. 4=0: G5@57 28A>:C ABV =5 1C;8 AB0B8AB8G=> 7=0GCI8<8. # 4>1@>2>;LFBV2 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 4>1@>2>;LFO<8 0=0;>3VG=>3> 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.# 4>1@>2>;LFV2 V7 F8@>7< ?5GV=:8 ;53:>3> B0 ?>3> ABC?5=O BO6:>ABV (:;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 4>1@>2>;LFO<8 0=0;>3VG=>3> 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 BO6:>3> ABC?5=O =5 282G0;0AO.

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

A=>2=V DV78:>-EVABV: :@C3;V 42>>?C;:V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, @>652>3> :>;L>@C.

"5@ABV. 2 @>:8.

#<>28 715@V30==O. □15@V30B8 ?@8 B52 =54>ABC?=>.

#?0:>2:0.

"01;5B:8 ?> 50 <3: ?> 1 01> ?> 2, 01> ?> 4 B01;5B:8 C 1;VAB5@V; ?> 1 1;VAB5@C 2:0@B>==V9 :>@>1FV. "01;5B:8 ?> 100 <3: ?> 1 01> ?> 4 B01;5B:8 C 1;VAB5@V; ?> 1 1;VAB5@C 2:0@B>==V9 :>@>1FV.

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

8@>1=8:. \$! V

VAF57=0E>465==O

-56/57, \$597 -, 5@=0 =40AB@V0; AB59B, 5@=0, !0;A5B, >0 403 722, =4VO.

002=8:. 2@> 09D:5@ B4.

VAF57=0E>465==O.1-9 ?>25@E, 26, \$>C15@BA ;59A, >=4>=, W1F7PP, 5;8:0 @8B0=VO.