

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

(OMIX)

!::04:
4VNG0 @5G>28=0: B078=C 3V4@>E;>@84;
1 :0?AC;0 78=C 3V4@>E;>@84C;
4>?>28=8: F5;N;>70 :@8AB0;VG=0, <5B0:@8;0B=>3> A>?>;V<5@C 48A?5@AVO, 3V?@>5;>70
(3V4@>:A8?@>?V;<5B8;F5;N;>70), ?@>?V;5=3;V:>;L, B0;L.;<03=VN AB50@0B, =0B@VN
;0C@8;AC;LD0B; >1>;>=:0 :0?AC;8: B8B0=C 4V>:A84 (171), EV=>;V=>289 6>2B89 (104), :0@<>W78=
(122), ?>=A> 4R (124), 65;0B8=.

V:0@AL:0 D>@<0. 0?AC;8 B25@4V, ?@>;>=3>20=>W 4VW.
A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 F8;V=4@8G=>W D>@<8 7 =5?@>7>@8<
:>@?CA>< 1V;>3> :>;L>@C B0 =5?@>7>@>N :@8H5G:>N G5@2>=>3> :>;L>@C, I> 3> 01> <0965
1V;>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, I> 70AB>A>2CNBLAO ?@8 4>1@>O:VA=V9 3V?5@?;07VW
?5@542>W 70;>78. =B03>=VAB8 α₁-04@5=5@3VG=8E @5F5?B>@V2. >4 "% G04C A02.

\$0@<0:>;>3VG=V 2;0AB82>ABV.
\$0@<0:>48=0
2> V :>=:C@5=B=> 1;>;CT ?>ABA8=0?B8G=V α₁-04@5=>@5F5?B>@8, 7>:@5<0 α_{1A} B0 α_{1D}, I>
7=0E>4OBLAO C 3;04:V9 2>W 70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8 C@5B@8. &5
?@872>48BL 4> 7=865==O B>=CAC 3;04:>W 2>W 70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8
C@5B@8 B0 4> ?>;V?H5==O 284V;5==O A5GV. 4=>G0A=> 7<5=HCNBLAO A8<8 >1AB@C:FVW B0
?>4@07=5==O, ?>2O70=V 7 4>1@>O:VA=>N 3V?5@?;07VTN ?5@542>W 70;>78 (CB@C4=5==O
?>G0B:C A5G>28?CA:0==O, ?>A;01;5==O AB@C<5=O A5GV, :@0?0==O ?VA;O 70:V=G5==O
A5G>28?CA:0==O, 2V4GCBBO =5?>2=>3> A?>@>6=5==O A5G>2>3> 7828 4> A5G>28?CA:0==O, ?>7828
4> A5G>28?CA:0==O C =VG=89 G0A, =52V4;:04=VABL A5G>28?CA:0==O).
/: ?@028;>, B5@0?52B8G=89 5D5:B @>72820TBLAO G5@57 2 B86=V 2V4 ?>G0B:C ?@89>2389 G0A
715@V30NBLAO ?@8 4>23>AB@>:>2>N N AB@82545==O EV@C@3VG=>W >?5@0FVW 01>
:0B5B5@870FVW.
=B03>=VAB8 α₁-04@5=>@5F5?B>@V2 <0NBL 740B=VABL 7=86C20B8 0@B5@V0;L=89 B8A: H;OE<
7=865==O B>=CAC ?5@8D5@8G=8E AC48=. "078= 2 4>1>2V9 4>7V 0,4 <3 =5 A?@8G8=OT ;:V=VG=>
28@065=>3> 7=865==O 0@B5@V0;L=>3> B8A:C.

\$0@<0:>:V=5B8:0.
A<>:BC20==O: B078= 4>1@5 2A<>:BCTBLAO 7V H;C=:>2>3> -:8H:>2>3> B@0:BC, 0 9>3>
1V>4>ABC?>=VABL AB0=>28BL<0965 100 %. A<>:BC20==O B078=C 2V41C20TBLAO 45I> ?>2V;L=VH5
?VA;O ?@89>@V4=VABL 2A<>:BC20==O 4>AO30TBLAO C B>;8 ?0FVT=B ?@89<0T 48= V B>9 A0<89
G0A ?VA;O ?@89>78=C <0T ;V=V9=89 E0@0:B5@.
VA;O ?@89>2>W 4>78 20 :>=F5=B@0FVO B078=C C ?;072V 4>AO30TBLAO ?@81;87=> G5@57 6 3>48=
0 AB01V;L=0 :>=F5=B@0FVO CB2>@NTBLAO =0 ?OBC 4>1C ?VA;O I>45==>3> ?@89>_max ?@8 FL> =0
42V B@5B8=8 28I>N 70 BC, I> CB2>@NTBLAO ?VA;O ?@89>2>W 4>78.
>7?>4V;: C G>;>2V:V2 B078= ?@81;87=> =0 99 % 7207CTBLAO 7 1V;:0<8 ?;07<8 :@>2V. 1T<
@>7?>4V;C ?@5?0@0BC =57=0G=89 (?@81;87=> 0,2 ;/:3).
5B01>;V7B078=C 3V4@>E;>@84 =5 ?V440TBLAO 5D5:BC ?5@H>3> ?@>E>465==O V ?>2V;L=>
<5B01>;V7CTBLAO C ?5GV=FV 7 CB2>@5==O< D0@<0:>;>3VG=> 0:B82=8E <5B01>;V7V2, I>
715@V30NBL 28A>:C A5;5:B82=VABL 4> α₁-04@5=>@5F5?B>@V2. V;LH0 G0AB8=0 0:B82=>W
@5G>28=8 ?@8ACB=O C :@>2V C =57
;V7B078= B0 9>3> <5B01>;V7B8 282>4OBLAO 7 >@30=V7 V7 A5G5N. @81;87=> 9 % 4>78 70;8H0TBLAO
C 283;04V =57W 4VNG>W @5G>28=8.
VA;O @07>2>3> ?@89>78 =F5=B@0FVW C ?;072V ?5@V>48 =0?V2282545==O 2V4?>2V4=>
AB0=>2;OBL ?@81;87=> 10 B0 13 3>48=.

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

>:070==O.

V:C20==O DC=:FV>=0;L=8E @>7;04V2 7 1>:C =86=VE A5G>28E H;OEV2 ?@84>1@>O:VA=V9 3V?5@?;07VW ?@>AB0B8.

@>B8?>:070==O.

V?5@GCB;82VABL 4> B078=C 3V4@>E;>@84C, 2;:NG0NG8 <548:0<5=B>7=>-V=4C:>20=89 0=3V>=52@>B8G=89 =01@O:, 01> 4> 1C4L-O:>W 7 4>?>28=; =002=VABL 2 0=0<=57V >@B>AB0B8G=>W 3V?>B5=7VW; BO6:0 ?5GV=:>20 =54>AB0B=VABL.

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

@8 >4=>G0A=>AC20==V B078=C 3V4@>E;>@84C 7 0B5=>;>;<, 5=0;0?@8;>;<, 01> B5>DV;V=> >V:0@AL:>W 270T<>4VW =5 2V47=0G0;>AO. 4=>G0A=5 70AB>AC20==O 7 F8<5B848=>< ?V428ICT, 0 7 DC@>A5< 7=86CT :>=F5=B@0FVN B078=C C ?;072V, 0;5 >A:V;L:8 FV @V2=V 70;8H0NBLAO 2<560E =>@<8, C A?5FV0;L=V9 :>@5:FVW 4>7C20==O B078=C =5<0T ?>B@518.

4>A;V465==OE in vitro 4V075?0<, ?@>?@0=>;>;, B@8E;>@<5BV0784, E;>@<048=>=, 078=C C ?;072V ;N48=8. >4V1=8< G8=>< B078= =5 7?@0=>;>;C, B@8E;>@<5BV0784C B0 E;>@<048=>=C C ?;072V ;N48=8.

@>B5 48;>D5=0: B0 20@D0@8= <>6CBL ?V428IC20B8 H284:VABL 5;V78=C.

4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 <>65 ?@8725AB8 4> 71V;LH5==O 2?;82C B078=C 3V4@>E;>@84C. 4=>G0A=5 70AB>AC20==O 7 :5B>:>=07>;> (2V4><89 A8;L=89 V=3V1VB>@ CYP3A4) ?@872>48;> 4> 71V;LH5==O AUC V !max 4> 2,8 V 2,2 2V4?>2V4=>.

"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :><1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 ?0FVT=B0< 7 =87L:8< <5B01>;V7<>< CYP2D6.

"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C :><1V=0FVW 7 A8;L=8<8 V ?> 4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C V ?@>:A5B8=C (A8;L=89 V=3V1VB>@ !YP2D6) ?@872>48BL 4> 71V;LH5==O !max V AUC 4> 1,3 V 1,6 2V4?>2V4=>, 0;5 F5 =5 T :;V=VG=> 7=0GCI8 4=>G0A=5 70AB>AC20==O 7 V=H8<8 α_1 -04@5=>1;>;:0B>@0<8 <>65 ?>A8;N20B8 3V?>B5=782=89 5D5:B.

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

/: V ?@8 70AB>AC20==V V=H8E α_1 -04@5=>1;>;:0B>@V2, 2 >:@5<8E 28?04:0E ?@8 70AB>AC20==V ?@5?0@0BC <>6;825 7=865==O 0@B5@V0;L=>3> B8A:C, I> <>65 V=>4V ?@8725AB8 4> 2B@0B8 A2V4><>ABV. @8 ?>O2V ?5@H8E >7=0: >@B>AB0B8G=>W 3V?>B5=7VW (70?0<>@>G5==O, A;01:VABL) ?0FVT=B<0T ?@8AVAB8 G8 ?@89=OB8 3>@87=>B0;L=5 ?>;>65==O 4> 7=8:=5==O 28I573040=8E A8

5@54 B8< O: @>?>G0B8 ;V:C20==O ?@5?0@0B<, A;V4 ?@>9B8 <548G=5 >1AB565==O 7 <5B>N 28O2;5==O V=H8E AC?CB=VE 70E2>@N20=L, I> <>6CBL A?@8G8=8B8 B0:V A0>W 70;>78. 5@54 ?>G0B:>< ;V:C20==O =5>1EV4=> ?@>25AB8 @5:B0;L=5 >1AB565==O ?5@542>W 70;>78 B0 ?@8 =5>1EV4=>ABV B5AB =0 287=0G5==O @V2=O A?5F8DVG=>3> 0=B835=0 ?5@542>W 70;>78 (PSA) 4> ?>G0B:C B0 G5@57 >4=0:>2V ?@>

@87=0G0B8 ?@5?0@0B ?0FVT=B0< V7 BO6:>N D>@<>N =8@:>2>W =54>AB0B=>ABV (;V@5=A :@50B8=V=C <10 <;/E2) =5>1EV4=> 7 >A>1;82>N >15@56=VABN, >A:V;L:8 :;V=VG=8E 4>A;V465=L 7 28:>@8AB0==O B078=C 3V4@>E;>@84C 4;O B0:8E ?0FVT=BV2 =5 ?@>2>48;8.

45O:8E ?0FVT=BV2, O:V ?@89<0;8 01> ?@89<0NBL B078=, ?V4 G0A EV@C@3VG=>3> 2B@CG0==O 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:><8 2V47=0G02AO A8=4@<< 0B>=VG=>W 7V=8FV (IFIS, 20@V0=B A8=4@>W 7V=8FV), I> <>65 AB0B8 ?@8G8=>N 71V;LH5==O :V;L:>ABV CA:;04=5=L ?V4 G0A G8 ?VA;O ?@>2545==O B0:>W >?5@0FVW.

/: ?@028;>, 70 1-2 B86=V ?5@54 ?@>2545==O< >?5@0FVW 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:> <8 @5:><5=4CTBLAO ?@8?8=8B8 ;V:C20==O B078=><, ?@>B5 :>@8ABL 2V4 ?@8?8=5==O ;V:C20==O B078=>< =0 40=89 G0A B>G=> =5 2AB0=>2;5=0. @> A8=4@<< 0B>=VG=>W 7V=8FV ?>2V4<<;O;>AO B0:>6 C ?0FVT=BV2, C O:8E ?@8?8=8;8 70AB>AC20==O B078=C ?@>BO3<< B@820;>3> G0AC 4> ?@>2545==O >?5@0B82=>3> 2B@CG0==O 7 ?@82>4C :0B0@0:B8.

?0FVT=BV2 ?5@54 ?;0=>2>N >?5@0FVTN :0B0@0:B8 G8 3;0C:><8 =5 @5:><5=4CTBLAO ?>G0B>:
?@89>78=C 3V4@>E;>@84C. @8 ?V43>B>2FV 4> >?5@0FVW EV@C@38 B0 >DB0;L<>;>38 <0NBL
4V7=0B8AO, G8 ?@89<02 (01> ?@89<0T) ?0FVT=B B078= 7 <5B>N ?>?5@5465==O <>6;828E
CA:;04=5=L, ?>2O70=8E V7 IFIS.

"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :><1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4
?0FVT=B0< 7 =87L:8< <5B01>;V7<>< CYP2D6.

"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C :><1V=0FVW 7 A8;L=8<8 V ?>
>2V4><;O;>AL ?@> 28?04:8 0;5@3VG=8E @50:FV9 =0 B078= C ?0FVT=BV2 7 =0O2=VABN 2 0=0<=57V
0;5@3VW =0 AC;LD0=V;0B@815@56=>ABV ?@8 70AB>AC20==V B078=C 3V4@>E;>@84C C
?0FVT=BV2, C O:8E @0=VH5 2V47=0G0;0AL 0;5@3VO =0 AC;LD0=V;0

0AB>AC20==O C ?5@V>4 203VB=>ABV B0 01> 3>4C20==O 3@C44N.

:070=89 4;O 70AB>AC20==O 6V=:0

\$5@B8;L=VABL.

V4 G0A ;V=VG=8E 4>A;V465=L B078=C ?@>B03>< :>@>B:>3> B0 B@820;>3> G0AC 2V47=0G0;8AO
?>@CH5==O 5O:C;OFVW. 8?04:8 ?>@CH5==O 5O:C;OFVW, @5B@>3@04=>W 5O:C;OFVW V
=54>AB0B=L>W 5O:C;OFVW 2V47=0G0;8AO C ?VA;O@5TAB@0FV=>4V.

**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==O I>4> 2?;82C ?@5?0@0BC =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> ?@0FN20B8
7 V=H8<8 <5E0=V7<0<8 =5 ?@>2>48;8. 4=0: ?0FVT=B8 <0NBL 1CB8 ?>?5@5465=V ?@> <>6;82VABL
28=8:=5==O 70?0<>@>G5==O.

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

5:><5=4>20=0 4>70 4;O 4>@>A;8E 1 :0?AC;0 I>45==>, ?VA;O A=V40=:C G8 ?VA;O ?5@H>3> ?@89>
2B0B8 FV;>N, =5 @>7;02C20B8, >A:V;L:8 F5 1C45 ?5@5H:>460B8 <>48DV:>20=>3> V=3@54VT=B0.
;O ?0FVT=BV2 7 =8@:>2>N =54>AB0B=VABN =5 ?>B@V1=0 :>@5:FVO 4>78. # ?0FVT=BV2 7
?5GV=:>2>N =54>AB0B=VABN ?>3> B0 A5@54=L>3> ABC?5=O B06:>ABV =5 ?>B@V1=0 :>@5:FVO
4>78 (482. B0:>6 «@>B8?>:070==O»).

VB8.

@5?0@0B =5 70AB>A>2C20B8 4VBO

57?5:0 B0 5D5:B82=VABL B078=C C 4VB59 =5 >FV=N20;0AL.

5@54>7C20==O.

!8<8.

5@54>7C20==O B078=C 3V4@>E;>@84C <>65 ?>B5=FV9=> A?@8G8=8B8 B06:C 3V?>B5=782=C 4VN.
"O6:0 3V?>B5=782=0 4VO 2V47=0G0;0AL ?@8 @V7=8E ABC?5=OE ?5@54>7C20==O.

V:C20==O.

28?04:C @V7:>3> 7=865==O B8A:C 2=0A;V4>: ?5@54>7C20==O A;V4 ?@>2>48B8 ?V4B@8: 28A>:>3>
ABC?5=O 72O7C20==O B078=C 7 1V;:0<8 ?;07<8 ?@>2545==O 35<>4V0;V7C T =02@O4 G8 4>FV;L=8
<5B>N ?@8?8=5==O ?>40;LH>3> 2A<>:BC20==O ?@5?0@0BC <>6=0 HBCG=> 28;;8:0B8 1;N20==O. @8
?5@54>7C20==V 7=0G=>N :V;L:VABN ?@5?0@0BC ?0FVT=BC =5>1EV4=> ?@>8B8 H;C=>: V7
70AB>AC20==O< 0:B82>20=>3> 2C3V;;O B0 =87L:>>A<>B8G=8E ?@=>A=8E 70A>1V2, B0:8E O:
AC;LD0B =0B@VN.

>1VG=V @50:FVW.

I>:C &! :70?0<>@>G5==O, 3>;>2=89 1V;L, =5?@8B><=VABL.

I>:C >@30=C 7>@C: 70BC<0=5==O 7>@C*, ?>@CH5==O 7>@C*.

I>:C A5@F52>-AC48==>W A8AB5<8: 2V4GCBBO A5@F518BBO, ?>ABC@0;L=0 3V?>B5=7VO.

I>:C 48E0;L=>W A8AB5<8: @8=VB, =>A>20 :@>2>B5G0*.

I>:C H;C=:>2>-.8H:>2>3> B@0:BC: 70?>@, 4V0@5O, =C4>B0, 1;N20==O.

I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: 28A8?, A25@1V6, :@>?82O=:0, 0=3V=>52@>B8G=89 =01@O.,
A8=4@>< !BV25=A0-6=>A=>0, @<=0 5@8B5<0*, 5:AD>;V0B82=89 45@<0B8B*.

I>:C @5?@>4C:B82=>W A8AB5<8: @>7;048 5O:C;OFVW, 2;:NG0NG8 @5B@>3@04=C 5O:C;OFVN V =54>AB0B=VABL 5O:C;OFVW.

030;L=V @>7;048: 0AB5=VO.

*- 2V47=0G0;8AO C ?VA;O@5TAB@0FV9=>4V.

V4 G0A ?VA;O@5TAB@0FV9=>3> =03;O4C >?8A0=V 28?04:8 V=B@0>?5@0FV9=>W =5AB01V;L=>ABV @094C6=>W >1>;>=:8 >:0 (A8=4@> 72C65=>W 7V=8FV) ?@8 >?5@0FVW 7 ?@82>4C :0B0@0:B8 B0 3;0C:>8 C ?0FVT=BV2, O:V ?@89<0;8 B078= (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

VA;O@5TAB@0FV9=89 4>A2V4: :@V< 28I52:070=8E ?>1VG=8E @50:FV9 ?>2V4<;O;>AL ?@> 28?04:8 DV1@8;OFVW ?5@54A5@4L, 0@8B5. A:V;L:8 ?@> 707=0G5=V 28?04:8 ?>2V4<;O;8AL A?>=B0==>, G0AB>BC ?>2V4<;5=L B0 @>;L B078=C C FL>

0@2=8:8 :0@<W78= (122) B0 ?>=A> 4R (124), I> 2E>4OBL 4> A:;04C >1>;>=:8 :0?AC;8, <6CBL A?@8G8=8B8 0;5@3VG=V @50:FVW.

"5@ABV. 3 @>:8.

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

#?0:>2:0.> 10 :0?AC; C 1;VAB5@V. 1 01> 3 1;VAB5@8 C ?0GFV 7 :0@B>=C.

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

8@>1=8:. @" «"5E=>;>3».

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

20300, #:@0W=0, '5@:0AL:0 >1;., #<0=L, 2C;8FO 0=CW;LAL:>3>, 1C48=>: 8.