

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

!,:04:

4VNGV @5G>28=8: 1 :0?AC;0
4>?>28=8: :0;LFVN 3V4@>D>AD0B, :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89, <03=VN AB50@0B;
>1>;>=:0 :0?AC;8 :A84 (171), 65;0B8=.

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

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

\$0@<0:>B5@0?52B8G=0 3@C?0. A8E>AB8>B@>?=V 70A>18. >4 "% N06B %.

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

\$0@<0:>48=0

?®-□ 4>@>2□ O :><1V=>20=89 ?@5?0@0B. :B82=8<8 :>=5=B0<8 ?@5?0@0BC T ?V@0F5B0<, F8;;VG=5
>EV4=5 γ-0<0A;O=>W :8A;>B8, V F8=0@878= A5;5:B82=89 0=B03>=VAB :0;LFVT28E :0=0;V2.
V@0F5B0< T =>>B@>?=8< 70A>1><, I> 4VT =0 <>7>;, ?>:@0ICNG8 :>3=VB82=V (?V7=020;L=V)
DC=:FVW, B0:V O: 740B=VABL 4> =02G0==O, ?&OBL, C2030, 0 B0:>6 @>7C<>2C ?@0F5740B=VABL.
5E0=V72C A8AB5ABV ?>H8@5==O 71C465==O C 3>;>2=>F8@:C;OFVW H;OE>< 2?;82C =0
@5>;>3VG=V E0@0:B5@8AB8:8 :@>2V, =5 A?@8G8=ONG8 ?@8 FL>@>7H8@N20;L=>W 4VW.
>:@0ICT 72 O7:8

&8=0@878= ?@83=VGCT A:>@>G5==O ;;VB8= 3;04:8E 20A:C;O@=8E <07V2 H;OE>< 1;>;C20==O
:0;LFVT28E :0=0;V2. >40B:>2> 4> ?@O<>3> :0;LFVT2>3> 0=B03>=V7@>GC20;L=C 4VN 207>0:B82=8E
@5G>28=, B0:8E O: =>@5?V=5D@8= V A5@>B>=V=, H;OE>< 1;>;C20==O :>=B@>;L>20=8E =8<8
@5F5?B>@V2 :0;LFVT28E :0=0;V2. ;>:040 =04E>465==O :0;LFVN 4> ;;VB8= 70;568BL 2V4 @V7=>284C
B:0=8=8, @57C;LB0B>< WW T 0=B8207>:>=AB@8:B>@=V 4VW 157 2?;82C =0 0@B5@V0;L=89 B8A: V
G0AB>BC A5@F528E A:>@>G5=L. &8=0@878= <>65 C ?>40;LH>;V?HC20B8 =54>AB0B=N
F8@:C;OFVN H;OE>< ?V428I5==O 5;0AB8G=>ABV <5<1@0=8 5@8B@>F8BV2 V 7=865==O 2O7:>ABV
:@>2V. 1V;LHCTBLAO ;;VB8==0 @578AB5=B=VABL 4> 3V?>:AVW. &8=0@878= ?@83=VGCT ABW
A8AB5<8, I> 2545 4> 28=8:=5==O =VAB03>><=8E @>7;04V2. &8=0@878= 70?>1V30T 28=8:=5==N
3>AB@8E =0?04V2 70?0<>@>G5==O.

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

@5?0@0B H284:> B0 ?>2=VABN 2A<>:BCTBLAO C H;C=:>2>-.8H:>2>AO30T ?V:>28E :>=F5=B@0FV9 C
?:072V G5@57 1 3>48=C ?VA;O >@0;L=>3> 70AB>AC20==O. >2=VABN<5B01>;V7CTBLAO.
2O7CTBLAO =0 91 % 7 1V;;<08 :@>2V. 60 % 282>48BLAO C =57<, 70;8H:>2V :V;L:>ABV V7 A5G5N C
283;04V <5B01>;VBV2.
0:A8<0;L=0 ?;07<>20 :>=F5=B@0FVO ?V@0F5B0AO30TBLAO G5@57 2-6 3>48=. V@0F5B0< 2V;L=>
?@>=8:0T :@V7L 35<0B>5=F5D0;VG=89 10@T@, 282>48BLAO V7 A5G5N C =57

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

>:070==O.

- %@>=VG=0 B0 ;0B5=B=0 =54>AB0B=VABL <>7:>2>3> :@>2>>1V3C ?@8 0B5@>A;;5@>7V B0
0@B5@V0;L=V9 3V?5@B5=7VW; 0=3V>48AB>=VG=89 VH5
- >ABB@02<0B8G=0 F5@51@0AB5=VO.
- =F5D0;>?0BVO @V7=>3> ?>E>465==O.
- A8E>>@30=VG=89 A8=4@>< 7 ?5@52060==O< ?>@CH5==O ?0<OBV B0 V=H8E :>3=VB82=8E
DC=:FV9 01> ?>@CH5==O 5<>FV9=>-2>;L>2>W AD5@8.
- 01V@8=B>?0BVW 70?0<>@>G5==O, HC< C 2CE0E, =C4>B0, 1;N20==O, =VAB03
- !8=4@>< 5=LT@0.
- @>DV;0:B8:0 :V=5B>7V2.

@>B8?>:070==O. V428I5=0 GCB;82VABL 4> ?V@0F5B04> 1C4L-O:>3> 4>?>3> :>=5=B0 ?@5?0@0BC;
V=482V4C0;L=0 GCB;82VABL 4> ?>EV4=8E ?V@>;V4>=C.
"O6:0=8@:>20=54>AB0B=VABL, 3>AB@5 ?>@CH5==O<>7:>2>3> :@>2>>1V3C (35<>@03VG=89
V=AC;LB), E>@50 %0=BV=3B>=0, ?0@:V=A>=V7<, ?V428I5==O 2=CB@VH=L>>G=>3> B8A:C, ?A8E>
<>B>@=5 71C465==O.
5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

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

@8 >4=>G0A=>3>;N B0 70AB>AC20==V ?@5?0@0BV2, I> ?@83=VGCNBL F5=B@0;L=C =5@2>2C
A8AB5

@5?0@0B ?>B5= FVNT 4VN =>>B@>?=8E, 0=B83V?5@B5=782=8E V AC48=>@>7H8@N20;L=8E
70A>1V2. 0AB>AC20==O @07>< V7 AC48=>@>7H8@N20;L=8<8 ?@5?0@0B0<8 ?>A8;NT 9>3> 4VN, 0
=0O2=VABL F8=0@878=C 7=86CT 0:B82=VABL 3V?5@B5=782=8E 70A>1V2.

?®-□4>@>2□O ?>A8;NT 0:B82=VABL B8@5>W4=8E 3>@<>=V2 V <>65 A?@8G8=8B8 B@5<>@ B0
=5A?>:V9.

V03=>AB8G=5 2B@CG0==O: G5@57 A2V9 0=B83VAB048BL 4> A:;04C ?@5?0@0BC, <>65 <0A:C20B8
?>78B82=V @50:FVW I>4> D0:B>@V2 @50:B82=>ABV H:V@8 ?@8 ?@>2545==V H:V@=>W ?@>18, B>
3> 28:>@8AB0==O A;V4 ?@8?8=8B8 70 4 4=V 4> WW ?@>2545==O.

@>B85?V;5?B8G=V ;V:0@AL:V 70A>18: =5 2V47=0G5=> 270T<>4VW 7 :0@10<075?V=><, D5=VB>W=>
<, D5=>10@1VB0;><, 20;L?@>0B>< =0B@VN (V=D>@<0FVO >A=>20=0 =0 2V4><8E 40=8E
70AB>AC20==O ?V@0F5B07V 20 <3/4>1C I>45==> ?@>B03>< 4 B86=V2).
>65 ?>A8;8B8 4VN ?5@>@0;L=8E 0=B8:>03C;O=BV2.

F5=>:C<0@>:.

E2>@8E V7 BO6:8< ?5@51V3>< @5F8482CNG>3> B@><1>7C 70AB>AC20==O ?V@0F5B0:8E 4>70E
(9,6 3/4>1C) =5 2?;820;> =0 4>7C20==O 0F5=>:C<0@>;C 4;O 4>AO3=5==O 7=0G5==O ?@>B@>
<1V=>2>3> G0AC (INR) 2,5-3,5, 0;5 ?@8 9>3> >4=>G0A=>AC20==V 2V47=0G0;>AO 7=0G=5 7=865==O
@V2=O 03@530FVW B@><1>F8BV2, @V2=O DV1@8=>35=C, D0:B>@V2 V;;51@0=40 (:>03C;OFV9=0
0:B82=VABL (VIII: C); :-D0:B>@ @VAB>F5B8=C (VIII: vW: Rco) B0 ?@>B5W= C ?;07VIII: vW: Ag)), 2
O7:>ABV :@>2V V ?;07<8 :@>2V.

\$0@<0:>:V=5B8G=V 270T<>4VW.

<>2V@=VABL 71V2 =87L:0, >A:V;L:8 90 % ?V@0F5B048BLAO C =57

In vitro ?V@0F5B0< =5 ?@83=VGCT F8B>E@>< 450 V7>D>@<8 CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1
V 4A9/11 C :>=F5=B@0FVW 142, 426, 1422

@8 :>=F5=B@0FVW 1422 CYP2A6 (21 %) V 34/5 (11 %). 4=0: @V25=LK; F8E 42>E CYP-V7><5@V2
4>AB0B=V9 ?@8 ?5@528I5==V 1422

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

8@:>20 =54>AB0B=VABL.

@5?0@0B 7 >15@56=VABN ?@87=0G0B8 ?0FVT=B0< V7 70E2>@N20==O<8 =8@>:. # 28?04:0E ;53:>W
01> ?>W =8@:>2>W =54>AB0B=>ABV @5:><5=4CTBLAO 7<5=H8B8 B5@0?52B8G=C 4>7C 01>
71V;LH8B8 V=B5@20; AC20==O<8, >A>1;82> O:I> :;V@5=A :@50B8=V=C < 60 <;/E2.

5GV=:>20 =54>AB0B=VABL.

@5?0@0B 7 >15@56=VABN ?@87=0G0B8 ?0FVT=B0< V7 70E2>@N20==O<8 ?5GV=:8. %2>@8< V7
?>@CH5==O<8 DC=:FVW ?5GV=:8 =5>1EV4=> A;V4:C20B8 70 7=0G5==O<8 ?5GV=:>28E D5@<5=BV2.

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

@8 4>23>B@820;V9 B5@0?VW C E2>@8E ;VB=L>3> 2V:C @5:><5=4CTBLAO @53C;O@=89 :>=B@>;L
70 ?>:07=8:0<8 DC=:FVW =8@>:, ?@8 =5>1EV4=>ABV A;V4 :>@53C20B8 4>7C 70;56=> 2V4

@57C;LB0BV2 4>A;V465==O :;V@5=AC :@50B8=V=C.

@>=8:0T G5@57 DV;LB@C20;L=V <5<1@0=8 0?0@0BV2 4;O 35<>4V0;V7C.

0AB>AC20==O ?@5?0@0BC A;V4 C=8:0B8 ?@8 ?>@DV@VW.

?;82 =0 ;01>@0B>@=V 0=0;V78.

@5?0@0B <>65 40B8 E8I=>??>78B82=89 @57C;LB0B ?@8 ?@>2545==V 4>?V=3>2>3> :>=B@>;N C
A?>@BA<5=V2, 0 B0:>6 ?@8 287=0G5==V @04V>0:B82=>3> 9>4C, 72060NG8 =0 =0O2=VABL 9>4>2
1>;>=FV :0?AC;8.

?;82 =0 03@530FVN B@><1>F8BV2.

7207:C 7 B8<, I> ?V@0F5B0< 7=86CT 03@530FVN B@><I>F8BV2, =5>1EV4=> 7>15@56=VABN
?@87=0G0B8 ?@5?0@0B E2>@8< V7 ?>@CH5==O< 35<>AB07C, 7V AB0=0<8, I> <>6CBL
AC?@>2>46C20B8AO :@>2>28;820<8 (28@07:0 H;C=:>2>:-8H:>2>3> B@0:BC), ?V4 G0A 25;8:8E
EV@C@3VG=8E >?5@0FV9 (2;:NG0NG8 AB<0B>;>3VG=V 2B@CG0==O), E2>@8< V7 A8<0<8
BO6:>W :@>2>B5GV 01> E2>@8<, O:V <0NBL 2 0=0<=57V 35<>@03VG=89 V=AC;LB; 0 B0:>6
?0FVT=B0<, O:V 70AB>A>2CNBL 0=B8:>03C;O=B8, B@<1>F8B0@=V 0=B803@530=B8, 2;:NG0NG8
=87L:V 4>78 0F5B8;A0;VF8;>2>W :8A;>B8.

/: V V=HV 0=B83VAB018, ?@-□4>@>2□O <>65 A?@8G8=OB8 ?>4@07=5==O 2 5?V30AB@0;L=V9
4V;O=FV; 70AB>AC20==O 9>3> ?VA;O W48<>65 7<5=H8B8 O28I0 ?>4@07=5==O H;C=:0.
!;V4 CB@84=>G0A=>3> 26820==O 0;:>3>;N 01> 0=B845?@5A0=BV2, >A:V;L:8 ?@5?0@0B <>65
A?@8G8=OB8 A>=;82VABL, >A>1;82> =0 A0<>G0B:C ;V:C20==O (482. @>74V; «70T<>4VO 7 V=H8<8
;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N. # ?5@V>4 203VB=>ABV 01>
3>4C20==O 3@C44N ?@5?0@0B =5 70AB>A>2C20B8. # @07V =5>1EV4=>ABV ;V:C20==O ?@5?0@0B>
< A;V4 ?@8?8=8B8 3>4C20==O 3@C44N.

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. !;V4 4>B@815@56=>ABV ?V4 G0A :5@C20==O 02B>B@0=A?>@B< 01> @>1>B8 7
V=H8<8 <5E0=V7<0<8, 72060NG8 =0 28=8:=5==O <>6;828E ?>1VG=8E @50:FV9 7 1>:C F5=B@0;L=>W
=5@2>2>W A8AB5<8.

!?!>AV1 70AB>AC20==O B0 4>78. 0?AC;8 ?@-4>@>2O 70AB>A>2C20B8 >@0;L=> ?VA;O W48, =5
@>76>2CNG8, 70?820NG8 2>4>N.

>@>A;8<
> 1-2 :0?AC;8 3 @078 =0 4>1C.

C@A ;V:C20==O 1-3 2V4 BO6:>ABV 70E2>@N20==O.

5 70AB>A>2C20B8 4>2H5 3 6;825 ?@>2545==O 2-3 :C@AV2 =0 @V:.

VB8. 5 70AB>A>2C20B8.

5@54>7C20==O.

!8<8: ?>A8;5==O ?@>O2V2 ?>1VG=>W 4VW ?@5?0@0BC. # ?>>48=>:8E 28?04:0E 3>AB@>3>
?5@54>7C20==O A?>AB5@V30;8AO 48A?5?A8G=V O28I0 (4V0@5O 7 :@>2N, 1V;L C 682>BV), 7<>ABV
2V4 A>=;82>ABV 4> ABC?>@C B0 :<8, 1;N20==O, 5:AB@0?V@0157A>==O, =5A?>:V9, 59D>@VO,
4@0BV2;82VABL, B@5<>@, @V4:> :>H<0@8, 30;NF8=0FVW, AC4<8.
V:C20==O: 28;:8:0B8 1;N20==O, ?@>25AB8 ?@><820==O H;C=:0 (1060=> ?@>BO3< ?5@H>W 3>48=8
?VA;O ?@89>), 70AB>AC20B8 0:B82>20=5 2C3V;;O. @>2>48B8 A8<0B8G=C B5@0?VN. >6;825
70AB>AC20==O 35<>4V0;V7C.

>1VG=V @50:FVW.

I>:C =5@2>2>W A8AB5<8: 3V?5@:V=57VO, 0B0:AVO, 3>;>2=89 1V;L, 157A>==O, 25AB81C;O@=V
@>7;048, 70?0<>@>G5==O, ?V428I5==O G0AB>B8 =0?04V2 5?V;5?AVW<>6;8289 @878: ?>3V@H5==O
?5@51V3C 5?V;5?AVW, ?>@CH5==O @V2=>2038, B@5<>@, 3V?5@A><=VO, ;5B0@3VO, 48A:V=57VO,
?0@:V=A>=V7<, 2B><;N20=VABL. "@820;5 70AB>AC20==O E2>@8< ;VB=L>3> 2V:C <>65 ?@8725AB8
4> @>728B:C 5:AB@0?V@0
I>:C VW A8AB5<8: 3V?5@GCB;82VABL, C B>

I>:C B@02=>3> B@0:BC: 2V4GCBBO ACE>ABV C @>BV, 48A?5?AVO, 014B0, 48A:>@B C 4V;O=FV
H;C=:0, 4V0@5O, E>;5AB0B8G=0 6>2BO=8FO, ?V428I5=5 A;8=>284V;5==O, =C4>B0, 1;N20==O.
I>:C H:V@8: 0=3V>=52@>B8G=89 =01@O:, 45@<0B8B8, A25@1V6, 28A8?0==O, :@>?82O=:0,
D>B>GCB;82VABL, 3V?5@3V4@>7 (?V428I5=0 ?VB;82VABL), ;8H0T?>4V1=89 :5@0B>7,5@8B5
<0B>7=89 2>2G0: B0 G5@2>=89 ?;5A:0B89 ;8H09.
A8EVG=V @>7;048: ?V428I5=0 71C4;82VABL, 7=5@2>20=VABL, 715=B565==O, A>;82VABL,
45?@5AVO, B@82>6=VABL, 30;NF8=0FVW.
I>:C :VAB:>2>-< O7>2>W A8AB5<8: @83V4=VABL< O7V2.
=HV: 0AB5=VO, AB0B525 71C465==O, 35<>@03VG=V @>7;048.
@8 B@820;>>48=>:8E 28?04:0E <>65 A?>AB5@V30B8AO 71V;LH5==O<0A8 BV;0.

"5@ABV.2 @>: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. 0?AC;8 B25@4V 30 (10×3), 60 (10×6) C 1;VAB5@0E 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, %0@:V2AL:0 >1;., %0@:V2, 2C;8FO (52G5=:0, 1C48=>: 22.