

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

"
(ATROGREL)

!;:04:

4VNG0 @5G>28=a: :;>?V4>3@5;L;
1 B01;5B:0 ?V4>3@5;L C 283;O4V :;>?V4>3@5;N 1VAC;LD0BC, C ?5@5@0EC=:C =0 100%
;>?V4>3@5;L - 75 <3;
4>?>28=8: =0B@VN :@>A:0@<5;>70, F5;N;>70 :@8AB0;VG=0, ;0:B>78 <=>3V4@0B, >;VO
@8F8=>20 3V4@>35=V7>20=0;
?;V2:>20 >I>;>=:0: 3V4@>:A8?@>?V;<5B8;F5;N;>70, ;0:B>78 <=>3V4@0B, B8B0=C
4V>:A84 (171), B@80F5B8=, :0@

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. □=B8B@><1>B8G=V 70A>18. >4 "1 01104.

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

>:070==O.

@>DV;0:B8:0 ?@>O2V2 0B5@>B@><1>7C:

□ C E2>@8E, O:V ?5@5=5A;8 V=D0@:B :0@40 (?>G0B>; :V:C20==O - G5@57 :V;L:0 4=V2,
0;5 =5 ?V7=VH5 =V6 G5@57 35 4=V2 ?VA;O 28=8:=5==O), VH5G0B>; :V:C20==O - G5@57
7 4=V2, 0;5 =5 ?V7=VH5 =V6 G5@57 6 C O:8E 4V03=>AB>20=> 70E2>@N20==O
?5@8D5@8G=8E 0@B5@V9;

□ C E2>@8E V7 3>AB@8< :>@>=0@=8< A8=4@>>

V7 3>AB@8< :>@>=0@=8< A8=4@>>< 157 ?V49>:0@40 157 7C1FO Q), C B>

V7 3>AB@8< V=D0@:B >< :0@40 7 ?V49><< A53<5=B0 ST C :><1V=0FVW 7

0F5B8;A0;VF8;>2>N :8A;>B>N (C E2>@8E, O:V >B@8

@>DV;0:B8:0 0B5@>B@><1>B8G=8E B0 B@><1>5<1>;VG=8E ?>4V9 ?@8 DV1@8;OFVW
?5@54A5@4L.

>?V4>3@5;L ?>:070=89 C :><1V=0FVW 7 0F5B8;A0;VF8;>2>N :8A;>B>N 4>@>A;8<

?0FVT=B0< 7 DV1@8;OFVTN ?5@54A5@4L, C O:8E VA=CT: I>=09<5=H5 >48= D0:B>@

@878:C 28=8:=5==O AC48==8E ?>4V9, ?@>B8?>:070==O 4>; :V:C20==O 0=B03>=VAB0<8

2VB02>B5G, 4;O ?@>DV;0:B8:8 0B5@>B@><1>B8G=8E B0 B@><1>5<1>;VG=8E ?>4V9, C B>

@>B8?>:070==O.

□ V428I5=0 GCB;82VABL 4> 4VNG>W @5G>28=8 01> 4> V=H8E :>5=BV2 ?@5?0@0BC;

□ BO6:0 ?5GV=:>20 =54>AB0B=VABL;

□ 3>AB@V :@>2>B5GV (2 B>G5@5?=V :@>2>28;828) B0 70E2>@N20==O, O:V

A?@8ONBL WE @>728B:C (=0?@8;:04, 28@07:>20 E2>@>10 H;C=:0 B0 420=04FOB8?0;>W

:8H:8 C AB04VW 703>AB@5==O, =5A?5F8DVG=89 28@07:>289 :>;VB).

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

>@>A;V B0 ?0FVT=B8 ;VB=L>3> 2V:C. @5?0@0B ?@87=0G0NBL ?> 1 B01;5BFV (75 <3) 1

@07 =0 4>1C =570;56=> 2V4 ?@89>

?0FVT=BV2 V7 3>AB@8< :>@>=0@=8< A8=4@>>< 157 ?V49> (=5AB01V;L=0

AB5=>:0@4VO 01> V=D0@:B :0@40 157 7C1FO Q =0) ;V:C20==O :;>?V4>3@5;5<

?>G8=0NBL 7 >4=>@07>2>W =020=B06C20;L=>W 4>78 300 <3, 0 ?>BV< ?@>4>26CNBL

4>7>N 75 <3 1 @07 =0 4>1C (7 0F5B8;A0;VF8;>2>N :8A;>B>N (!) C 4>7V 75-325 <3 =0 4>1C).

A:V;L:8 70AB>AC20==O 1V;LH 28A>:8E 4>7 !?V428ICT @878: :@>2>B5GV, @5:>

<5=4CTBLAO =5 ?5@528IC20B8 4>7C !100 <3. ?B8<0;L=0 B@820;VABL ;V:C20==O D>@<0;L=> =5 2AB0=>2;5=0. 57C;LB0B8 4>A;V465=L A2V4G0BL =0 :>@8ABL 70AB>AC20==O ?@5?0@0BC 4> 12

?0FVT=BV2 V7 3>AB@8< V=D0@:B<< :0@40 7 ?V49><< A53<5=B0 ST :;>?V4>3@5;L ?@87=0G0NBL ?> 75 <3 1 @07 =0 4>1C, ?>G8=0NG8 7 >4=>@07>2>W =020=B06C20;L=>W 4>78 300 <3 C :><1V=0FVW 7 !, 7 70AB>AC20==O< B@><1>;VB8G=8E ?@5?0@0BV2 01> 157 =8E. V:C20==O ?0FVT=BV2 2V:> 2V4 75 @>:V2 ?>G8=0NBL 157 =020=B06C20;L=>W 4>78 :;>?V4>3@5;N. ><1V=>20=C B5@0?VN A;V4 ?>G8=0B8 O:>>30 @0=VH5 ?VA;O ?>O28 A84>26C20B8 ?@8=09<=V 4 B86=V. >@8ABL 2V4 70AB>AC20==O :><1V=0FVW :;>?V4>3@5;N 7 !?>=04 4 B86=V ?@8 FL>@N20==V =5 282G0;0AO.

0FVT=B0< V7 DV1@8;OFVTN ?5@54A5@4L :;>?V4>3@5;L 70AB>A>2CNBL C @07>2V9 4>1>2V9 4>7V 75 <3. 07>< V7 :;>?V4>3@5;5< A;V4 @>?>G8=0B8 70AB>AC20==O !(C 4>7V 75-100 <3 =0 4>1C) B0 ?@>4>26C20B8 9>3>.

@07V ?@>?CA:C 4>78:

O:I> 7 <><5=BC, :;>;8 ?>B@V1=> 1C;> ?@89<0B8 G5@3>2C 4>7C, <8=C;> <5=H5 12 3>48= ?0FVT=B ?>28=5= =5309=> ?@89=0B8 ?@>?CI5=C 4>7C, 0 =0ABC?>C 4>7C 265 ?@89<0B8 C 728G=89 G0A;

O:I> <8=C;> 1V;LH5 12 3>48=, ?0FVT=B ?>28=5= ?@89<0B8 =0ABC?>C 4>7C C 728G=89 G0A B0 =5 ?>42>N20B8 4>7C 7 <5B>N :>?CI5=>W 4>78.

\$0@<0:> 35=5B8:0. >H8@5=VABL 0;5;59 CYP2C19, O:V A?@8G8=ONBL ?@>?B8<0;L=89 @568< 4>7C20==O C >AV1 V7 ?>A;01;5=8< <5B01>;V7<>< CYP2C19 ?>:8 I> =5 2AB0=>2;5=89.

VB8. 57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ;>?V4>3@5;N 4VBO< =5 2AB0=>2;5=V, B> ?@5?0@0B =5 A;V4 70AB>A>2C20B8 4VBO<.

8@:> 20 =54>AB0B=VABL. "5@0?52B8G=89 4>A2V4 70AB>AC20==O ?@5?0@0BC ?0FVT=B0 < V7 =8@:>2>N =54>AB0B=VABN >1<565=89 (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

5GV=:> 20 =54>AB0B=VABL. "5@0?52B8G=89 4>A2V4 70AB>AC20==O ?@5?0@0BC ?0FVT=B0< V7 70E2>@N20==O<8 ?5GV=:8 A5@54=L>W BO6:>ABV B0 <>6;82VABN 28=8=:5==O 35<>@03VG=>3> 4V0B57C >1<565=89 (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

>1VG=V @50:FVW.

091V;LH ?>H8@5=>N ?>1VG=>N @50:FVTN 1C;0 :@>2>B5G0, O:0 =09G0ABVH5

A?>AB5@V30;0AO 2 ?5@H89

@>2 B0 ;V

□ B@><1>F8B>?5=VO, ;59:>?5=VO, 5>78=>DV;VO;

□ =59B@>?5=VO, 2;:NG0NG8 BO6:C =59B@>?5=VN;

□ B@><1>B8G=0 B@><1>F8B>?5=VG=0 ?C@?C@0 (TT) (482. @>74V; «A>1;82>ABV 70AB>AC20==O»), 0?;0AB8G=0 0=5?5=VO, 03@0=C;>F8B>7, BO6:0 B@><1>F8B>?5=VO, 3@0=C;>F8B>?5=VO, 0=5

□ A8@>20B:>?>4V1=89 A8=4@<, 0=0DV;0:B>W4=V/0=0DV;0:B8G=V @50:FVW;

□ ?5@5E@5A=0 3V?5@GCB;82VABL ?>?V@848=V2 (B0:8E O: BV:;>?V48=, ?@0AC3@5;L) (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

A8EVG=V ?>@CH5==O

□ 30;NF8=0FVW, A?;CB0=VABL A2V4>>ABV.

5@2>20 A8AB5<0

□ 2=CB@VH=L>G5@5?=V :@>2>B5GV (C 45O:8E 28?04:0E V7 ;5B0;L=8< =0A;V4:><), 3>;>2=89 1V;L, ?0@5AB57VO, 70?0<>@>G5==O;

□ 7

0B>;>3VO >@30=V2 7>@C

□ :@>2>B5G0 2 4V;O=:C >:0 (:>=N=:B820;L=0, >:C;O@=0, @5B8=0;L=0).

0B>;>3VO 2CE0 B0 ;01V@8=BC

□ 25@B83>.

!C48==V @>7;048

□ 35<0B><0;

□ BO6:0 :@>2>B5G0, :@>2>B5G0 7 >?5@0FV9=>W @0=8, 20A:C;VB,
0@B5@V0;L=0 3V?>B5=7VO.

5A?V@0B>@=V, B>@0:0;L=V B0<54V0AB8=0;L=V ?>@CH5==O

□ =>A>20 :@>2>B5G0;

□ :@>2>B5GV 7 48E0;L=8E H;OE2 (:@>2>E0@:0==O, ;535=52V :@>2>B5GV), 1@>=E>A?07
<, V=B5@AB8FV0;L=89 ?=52<>=VB, 5>78=>DV;L=0 ?=52<>=VO.

(;C=:>2>-.8H:>2V @>7;048

□ H;C=:>2>-.8H:>2V :@>2>B5GV, 4V0@50, 014>

□ 28@07:0 H;C=:0 B0 420=04FOB8?0;>W :8H:8, 30AB@8B, 1;N20==O, =C4>B0, 70?>@,
<5B5>@87<;

□ @5B@>?5@8B>=50;L=89 :@>2>28;82;

□ H;C=:>2>-.8H:>2V B0 @5B@>?5@8B>=50;L=V :@>2>B5GV 7 ;5B0;L=8< =0A;V4:<,&br/>?0=:@50B8B, :>;VB (7>:@5<0 28@07:>289 01> ;VF8B0@=89), AB><0B8B.

5?0B>1V;V0@=0 A8AB5<0

□ 3>AB@0 ?5GV=:>20 =54>AB0B=VABL, 35?0B8B, 0=><0;L=V @57C;LB0B8 ?>:07=8:V2
DC=:FVW ?5GV=:8.

(:V@0 B0 ?V4H:V@=0 ;:VB:>28=0

□ ?V4H:V@=89 :@>2>28;82;

□ 28A8?, A25@1V6, 2=CB@VH=L>H:V@=V :@>2>28;828 (?C@?C@0);

□ 1C;L>7=V 45@<0B8B8, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, A8=4@< !BV25=A0-
6>=A>=0, @<=0 5@8B5<0, 0=3V>=52@>B8G=89 =01@O:, 5@8B5<0B>7=89 28A8?,
:@>?82O=:0, <548:0<5=B>7=89 A8=4@< 3V?5@GCB;82>ABV, <548:0<5=B>7=0 28A8?:0 7
5>78=>DV;VTN B0 A8AB5<=8<8 ?@>O20<8 (DRESS-A8=4@<), 5:75<0, ?>A:89 ;8H09.

VAB:>2><O7>20 A8AB5<0, A?>;CG=0 B0 :VAB:>20 B:0=8=8

□ <O7>2>-A:5;5B=V :@>2>28;828 (35<0@B@>7), 0@B@8B, 0@B@0;3VO,

8@:8 B0 A5G>284V;L=0 A8AB5<0

□ 35<0BC@VO;

□ 3;><5@C;>=5D@8B, ?V428I5==O @V2=O :@50B8=V=C 2 :@>2V.

030;L=89 AB0=

□ 30@OG:0.

01>@0B>@=V 4>A;V465==O

□ ?>4>265==O G0AC :@>2>B5GV, 7=865==O :V;L:>ABV =59B@>DV;V2 V B@>1>F8BV2.

5@54>7C20==O.

!8<8: ?>4>265==O G0AC :@>2>B5GV 7 =0ABC?=8<8 CA:;04=5==O<8.

V:C20==O: A8<0B8G=5. !?5FV0;L=>3> 0=B84>BC =5<0T. @8 =5>1EV4=>ABV =5309=>W

:>@5:FVW ?>4>265=>3> G0AC :@>2>B5GV 4VN ;;>?V4>3@5;N <>6=0 CAC=CB8

B@0=ADC7VTN B@><1>F8B0@=>W <0A8.

0AB>AC20==O 2 ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

'5@57 2V4ACB=VABL ;;V=VG=8E 40=8E 70AB>AC20==O ;;>?V4>3@5;N C ?5@V>4

203VB=>ABV =5 @5:><5=4CTBLAO ?@87=0G0B8 ?@5?0@0B 203VB=8< 6V=0

52V4><>, G8 5:A:@5BCTBLAO ;;>?V4>3@5;L C 3@C4=5 <>;>:, B< 3>4C20==O 3@C44N

A;V4 ?@8?8=8B8.

VB8.

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ;>?V4>3@5;N 4VBO< =5 2AB0=>2;5=V, B>

?@5?0@0B =5 A;V4 70AB>A>2C20B8 4VBO<.

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

@>2>B5G0 B0 35<0B>;>3VG=V @>7;048.

'5@57 @878: @>728B:C :@>2>B5GV B0 35<0B>;>3VG=8E ?>1VG=8E @50:FV9 A;V4 =5309=>

?@>25AB8 @>73>@=CB89 0=0;V7 :@>2V B0/01> V=HV 2V4?>2V4=V B5AB8, O:I> ?V4 G0A

70AB>AC20==O ?@5?0@0BC A?>AB5@V30NBLAO A8<8, I> A2V4G0BL ?@> <>6;82VABL

:@>2>B5GV.!: V V=HV 0=B8B@><1>F8B0@=V 70A>18, ;;>?V4>3@5;L A;V4 7

>15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< 7 ?V428I5=8< @878:>< :@>2>B5GV 2=0A;V4>:
B@02<8, EV@C@3VG=>3> 2B@CG0==O 01> V=H8E ?0B>;>3VG=8E AB0=V2, 0 B0:>6 C
@07V 70AB>AC20==O ?0FVT=B0<8 0F5B8;A0;VF8;>2>W :8A;>B8 (!), 35?0@8=C,
V=3V1VB>@V2 3;V:>?@>B5W=C IIb/III0 01> =5AB5@>W4=8E ?@>B870?0;L=8E
?@5?0@0BV2, C B>@V2 &-2. 5>1EV4=> C206=> AB568B8 70 ?@>O20<8 C ?0FVT=BV2 A8
2>B5GV, C B>20=>W :@>2>B5GV, >A>1;82> C ?5@HV B86=V ;V:C20==O B0/01> ?VA;O
V=207V9=8E ?@>F54C@ =0 A5@FV B0 EV@C@3VG=8E 2B@CG0=L. 4=>G0A=5
70AB>AC20==O ;>?V4>3@5;N 7 ?5@>@0;L=8<8 0=B8:>03C;O=B0<8 =5 @5:><5=4CTBLAO,
>A;V;L:8 2V=<>65 ?>A8;8B8 V=B5=A82=VABL :@>2>B5G (482. @>74V; «70T>4VO 7 V=H8
<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

28?04:C ?;0=>2>3> EV@C@3VG=>3> 2B@CG0==O, O:I> 0=B8B@><1>B8G=89 5D5:B T B8
2> =51060=8<, ;V:C20==O ;>?V4>3@5;5< A;V4 ?@8?8=8B8 70 7 4=V2 4> >?5@0FVW.
0FVT=B8 ?>28==V ?>2V4<<;OB8 ;V:0@V2 V AB<0B>;>3V2 ?@> B5, I> 2>=8 ?@89<0NBL
;>?V4>3@5;L, ?5@54 ?@87=0G5==O< W< 1C4L-O:>W >?5@0FVW 01> ?5@54
70AB>AC20==O< =>2>3> ;V:0@AL:>3> 70A>1C. ;>?V4>3@5;L ?>4>26CT B@820;VABL
:@>2>B5GV, B>3> A;V4 >15@56=> 70AB>A>2C20B8 ?0FVT=B0< 7 ?V428I5=8< @878:><
:@>2>B5GV (>A>1;82> H;C=:>2>-.8H:>2>W B0 2=CB@VH=L>>G=>W).
0FVT=BV2 A;V4 ?>?5@548B8, I> ?V4 G0A ;V:C20==O ;>?V4>3@5;5< (>:@5<< 01> C :>
<1V=0FVW 7 !):@>2>B5G0 <<65 7C?8=OB8AO ?V7=VH5, =V6 728G09=>, I> W< =5>1EV4=>
>?2V4<<;OB8 ;V:0@O ?@> :>65= 28?04>: =5728G=>W (70 ;>:0;V70FVTN G8 B@820;VABN)
:@>2>B5GV.

"@><1>B8G=0 B@><1>F8B>?5=VG=0 ?C@?C@0 (""").
C65 @V4:> A?>AB5@V30;8AO 28?04:8 B@><1>B8G=>W B@><1>F8B>?5=VG=>W
?C@?C@8 (TT) ?VA;O 70AB>AC20==O ;>?V4>3@5;N, V=>4V =02VBL ?VA;O 9>3>
:>@>B:>G0A=>3> 70AB>AC20==O. ""?@>O2;OTBLAO B@><1>F8B>?5=VTN B0
0=3V>?0B8G=>N 35<>;VB8G=>N 0=5;>3VG=8<8 ?@>O20<8, 48ADC=:FVTN =8@>: 01> ;8E>
<0=:>N. TTT ?>B5=FV9=> ;5B0;L=8< AB0=><, I> ?>B@51CT =5309=>3> ;V:C20==O, 7>:@5<0
?;07<>D5@57>

01CB0 35<>DV;VO.
>2V4<<;O;>AO ?@> 28?04:8 @>728B:C =01CB>W 35<>DV;VW ?VA;O 70AB>AC20==O
;>?V4>3@5;N. # 28?04:0E ?V4B25@465=>3> V7>;L>20=>3> 71V;LH5==O "" (0:B82>20=>3>
G0AB:>2>3> B@><1>?;0AB8=>2>3> G0AC), I> AC?@>2>46CTBLAO 01> =5
AC?@>2>46CTBLAO :@>2>B5G5N, ?8B0==O ?@> 4V03=>ABC20==O =01CB>W 35
<>DV;VW ?>28=> 1CB8 @>73;O=CB>. 0FVT=B8, 7 ?V4B25@465=8< 4V03=>7>< =01CB>W
35<>DV;VW ?>28==V 7=0E>48B8AO ?V4 =03;O4<<;V:0@O V >B@8AC20==O ;>?V4>3@5;N
>?28=> 1CB8 ?@8?8=5=>.

5I>402=> ?5@5=5A5=89 VH5
'5@57 =54>AB0B=VABL 40=8E =5 @5:><5=4CTBLAO ?@87=0G0B8 ;>?V4>3@5;L C ?5@HV
7 4=V2 ?VA;O 3>AB@>3> VH53> V=AC;LBC.
&8B>E@>< 450 2 !19 (CYP2C19). \$0@<0:>35=5B8:0.
?0FVT=BV2 V7 35=5B8G=> 7=865=>N DC=:FVTN CYP2C19 A?>AB5@V30TBLAO <5=H0
:=F5=B@0FVO 0:B82=>3> <5B01>;VBC ;>?V4>3@5;N C ?;072V B0 <5=H 28@065=89
0=B8B@><1>F8B0@=89 5D5:B, :@V< B>3>, C =8E 7=0G=> G0ABVH5 28=8:0NBL A5@F52->
AC48==V CA:;04=5==O ?VA;O V=D0@:BC:0@40 ?>@V2=O=> 7 ?0FVT=B0<8 7 =>@<0;L=8<
DC=:FV>=C20==O< CYP2C19.

A;V;L:8 ;>?V4>3@5;L<5B01>;V7CTBLAO 4> CB2>@5==O A2>3> 0:B82=>3> <5B01>;VBC
G0AB:>2> ?V4 4VTN CYP2C19, B> 70AB>AC20==O ?@5?0@0BV2, O:V 7=86CNBL
0:B82=VABL FL>3> D5@<5=BC, =09V<>2V@=VH5, ?@872545 4> 7<5=H5==O
:=F5=B@0FVW 0:B82=>3> <5B01>;VBC ;>?V4>3@5;N C ?;072V. "0: O: ;V=VG=5 7=0G5==O
FVTW 270T<>4VW =5 7OA>20=5, A;V4 C=8:0B8 >4=>G0A=>3> 70AB>AC20==O
?@5?0@0BV2, O:V ?@83=VGCNBL 0:B82=VABL CYP2C19 (482. @>74V; «70T>4VO 7 V=H8
<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

5@5E@5A=0 @50:B82=VABL ?>?V@848=V2.
0FVT=BV2 A;V4 ?5@52V@8B8 I>4> =0O2=>ABV 2 0=0<=57V 3V?5@GCB;82>ABV 4> V=H8E
BVT=>?V@848=V2 (B0:8E O: BV:>?V48=, ?@0AC3@5;L), >A;V;L:8 =04E>48;8 ?>2V4>

<;5==O ?@> ?5@5E@5A=C 0;5@3VN ?>?V@848=V2 (482. @>74V; <<>1VG=V @50:FVW»).

0AB>AC20==O BVT=>?V@848=V2 <>65 ?@8725AB8 4> 28=8:=5==O 2V4 ;53:8E 4> 206:8E

0;5@3VG=8E @50:FV9, B0:8E O: 28A8?0==O, =01@O: 2V=:5, 01> 35<0B>;>3VG=8E @50:FV9,

B0:8E O: B@><1>F8B>?5=VO V =59B@>?5=VO. 0FVT=B8, O:V 2 <8=C;>

>@CH5==O DC=:FVW =8@>:.

"5@0?52B8G=89 4>A2V4 70AB>AC20==O ;;>?V4>3@5;N ?0FVT=B0< V7 =8@:>2>N

=54>AB0B=VABN >1<565=89, B>

>@CH5==O DC=:FVW ?5GV=:8.

>A2V4 70AB>AC20==O ?@5?0@0BC ?0FVT=B0< V7 70E2>@N20==O<8 ?5GV=:8

A5@54=L>W B06:>ABV B0 <>6;82VABN 28=8:=5==O 35<>@03VG=>3> 4V0B57C >1

<565=89. ">

>?>28=8.

@5?0@0B 7C. 0FVT=B0< 7 @V4:>N A?04:>2>N =5?5@5=>A878, 45DVF8B>< ;0:B078 0??0,

?>@CH5==O< <0;L01A>@1FVW 3;N:>78-30;0:B>78 =5 A;V4 70AB>A>2C20B8 40=89

?@5?0@0B.

@5?0@0B ;VN @8F8=>2C 3V4@>35=V7>20=C, O:0 <>65 A?@8G8=8B8 @>7;04 H;C=:0 B0

4V0@5N.

/:I> ?0FVT=B 701C2 ?@89=OB8 4>7C ?@5?0@0BC V <8=C;> <5=H5 12 3>48= ?VA;O

?;0=>2>3> ?@89> ?@5?0@0B =5>1EV4=> ?@89=OB8 O:=09H284H5, ?VA;O G>3> =0ABC?=C

4>7C A;V4 ?@89=OB8 2G0A=>. /:I> <8=C;> 1V;LH5 12 3>48= A;V4 ?@>?CAB8B8 ?@89<

701CB>W 4>78 V ?@89=OB8 2G0A=> =0ABC?=C 4>7C ?@5?0@0BC. 54>?CAB8<> ?@89<0B8

?>42V9=C 4>7C ?@5?0@0BC.

V4 G0A ;V:C20==O ?@5?0@0B< =5 A;V4 26820B8 0;:>3>;L G5@57 ?V428I5==O @878:C

H;C=:>2>.:8H:>2>W :@>2>B5GV.

A>1;82V 70AB5@565==O I>4> 2840;5==O 70;8H:V2 B0 2V4E>4V2.

C4L-O:89 =528:>@8AB0=89 ?@5?0@0B 01> 2V4E>48 ?>B@V1=> 7=8I8B8 2V4?>2V4=> 4>

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.

@5?0@0B =5 2?;820T 01> <0T =57=0G=89 2?;82 =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 (482. @>74V; <<>1VG=V

@50:FVW»).

70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

5@>@0;L=V 0=B8:>03C;O=B8: >4=>G0A=5 70AB>AC20==O ;;>?V4>3@5;N 7 ?5@>@0;L=8

<8 0=B8:>03C;O=B0<8, 2 B><, =5 @5:><5=4CTBLAO, >A;V;L:8 B0:0 :<1V=0FVO <>65

?>A8;8B8 V=B5=A82=VABL :@>2>B5GV.

=3V1VB>@8 3;V:>?@>B5W=C Iib/IIIa: ;;>?V4>3@5;L A;V4 7 >15@56=VABN ?@87=0G0B8

?0FVT=B0< V7 ?V428I5=8< @878:<< :@>2>B5GV G5@57 B@02<8, >?5@0FVW 01> V=HV

?0B>;>3VG=V AB0=8, ?@8 O:8E >4=>G0A=> 70AB>A>2CNBL V=3V1VB>@8

3;V:>?@>B5W=C Iib/IIIa.

F5B8;A0;VF8;>20 :8A;>B0 (A!): 0F5B8;A0;VF8;>20 :8A;>B0 =5 7@=>W 4VW ;;>?V4>3@5;N =0

\$-V=4C:>20=C 03@530FVN B@><1>F8BV2, 0;5 ;;>?V4>3@5;L ?>A8;NT 4VN !=0 03@530FVN

B@><1>F8BV2, V=4C:>20=C :>;035=>B5 >4=>G0A=5 70AB>AC20==O 500 <3 A!42VGV =0

4>1C ?@>B03>< >4=>3> 4=O =5 28;:8:02 7=0G=>3> 71V;LH5==O G0AC :@>2>B5GV,

?>4>265=>3> 2=0A;V4>: ?@89>?V4>3@5;N. A;V;L:8 <>6;825 ?V428I5==O @878:C

:@>2>B5GV, >4=>G0A=5 70AB>AC20==O F8E ?@5?0@0BV2 ?>B@51CT >15@56=>ABV.

4=0: T 4>A2V4 70AB>AC20==O ;;>?V4>3@5;N B0 !@07<< ?@>B03>< ?5@V>4C 4> >4=>3>

@>:C.

5?0@8=: C 4>A;V465==V, ?@>2545=>@>28E 4>1@>2>;LFV2, 70AB>AC20==O ;;>?V4>3@5;N

=5 ?>B@51C20;> 778 35?0@8=C B0 =5 7 2?;82 35?0@8=C =0 :>03C;OFVN. 4=>G0A=5

70AB>AC20==O 35?0@8=C =5 7 V=3V1CNGC 4VN ;;>?V4>3@5;N =0 03@530FVN B@>

<1>F8BV2. A;V;L:8 <>6;820 D0@<0:>48=0?V4>3@5;5< V 35?0@8=<< V7 ?V428I5==O<

@878:C :@>2>B5GV, >4=>G0A=5 70AB>AC20==O F8E ?@5?0@0BV2 ?>B@51CT

>15@56=>ABV.

"@><1>;VB8G=V 70A>18: 157?5:C AC?CB=L>3> 70AB>AC20==O ;;>?V4>3@5;N,
DV1@8=>A?5F8DVG=8E 01> DV1@8=>=5A?5F8DVG=8E B@><1>;VB8G=8E 70A>1V2 V
35?0@8=C >FV=N20;8 70 CG0ABN ?0FVT=BV2 7 3>AB@8< V=D0@:B>< :0@40. '0AB>B0
>O28 ;;V=VG=> 7=0GCI>W :@>2>B5GV 1C;0 ?>4V1=>N 4> G0AB>B8 ?>O28, I>
A?>AB5@V30;0AO ?@8 AC?CB=L><1>;VB8G=8E 70A>1V2 V 35?0@8=C 7 A!
5AB5@>W4=V ?@>B870?0;L=V ?@5?0@0B8 (): C 4>A;V465==V, ?@>2545=>@>28E
4>1@>2>;LFOE, >4=>G0A=5 70AB>AC20==O ;;>?V4>3@5;N B0 =0?@>:A5=C 71V;LHC20;>
:V;L:VABL ?@8E>20=8E H;C=>2>:-8H:>28E :@>2>B5G. 4=0: G5@57 2V4ACB=VABL
4>A;V465=L I>4> 270T<>4VW ?@5?0@0BC 7 V=H8<8 4>B5?5@ =5 70A>20=>, G8 7@>AB0T
@878: H;C=>2>:-8H:>2>W :@>2>B5GV ?@8 70AB>AC20==V ;;>?V4>3@5;N 7 V=H8<8 . ">
1EV4=0 >15@56=VABL ?@8 >4=>G0A=>AC20==V, C B>@V2 &-2, 7 ;;>?V4>3@5;5
4=>G0A=5 70AB>AC20==O V=H8E ?@5?0@0BV2: >A;V;L:8 ;;>?V4>3@5;L
<5B01>;V7CTBLAO 4> CB2>@5==O A2>3> 0:B82=>3> <5B01>;VBC G0AB:>2> ?V4 4VTN
CYP2C19, B> 70AB>AC20==O ?@5?0@0BV2, O:V 7=86CNBL 0:B82=VABL FL>3> D5@
<5=BC, =09V<>2V@=VH5, ?@872545 4> 7=865==O :>=F5=B@0FVW 0:B82=>3> <5B01>;VBC
;;>?V4>3@5;N C ?;072V. ;V=VG=5 7=0G5==O FVTW 270T<>4VW =5 70A>20=5, B>
4=>G0A=>3> 70AB>AC20==O ?@5?0@0BV2, O:V ?@83=VGCNBL 0:B82=VABL CYP2C19.
> ?@5?0@0BV2, I> ?@83=VGCNBL 0:B82=VABL CYP2C19, =0;560BL><5?@07>;, 57>
<5?@07>;, D;C2>:A0:A5B8=, <>:;>15@8:>=07>;, D;C:>=07>;, B8:;>?V48=,
F8?@>D;>:A0F8=, F8<5B848=, :0@10<075?V=, >:A:0@1075?V= B0 E;>@0;
=3V1VB>@8 ?@>B>==>W ?>5D5:B82=VABL 0=B8B@><1>B8G=>W 4VW ;;>?V4>3@5;N
<>65 7=86C20B8AO <0965 =0?>;>28=C ?@8 :><1V=0FVW 7. %>G0 ABC?V=L ?@83=VG5==O
0:B82=>ABV CYP2C19 ?V4 4VTN @V7=8E ?@5?0@0BV2, I> =0;560BL 4> ;;0AC, =5 T
>4=0:>28<, 4>A;V465==O 2:07CNBL =0 VA=C20==O 270T<>4VW ?@0:B8G=> 7 CAV<0
?@54AB02=8:0<8 FL>3> ;;0AC. @8 FL>71V6=VABL ?@89>ABV ;;>?V4>3@5;N. ">
4=>G0A=>3> 70AB>AC20==O, 70 28=OB:>< 28?04:V2, :>;8 F5 T 01A>;NB=> =5>1EV4=8
>:07V2 B>3>, I> V=HV ?@5?0@0B8, O:V 7<5=HCNBL ?@>4C:FVN :8A;>B8 C H;C=:C,
=0?@8;;04
2-1;>:0B>@8 (:@V< F8<5B848=C, O:89 ?@83=VGCT 0:B82=VABL CYP2C19)01> 0=B0F848,
2?;820NBL =0 0=B8B@><1>F8B0@=C 0:B82=VABL ;;>?V4>3@5;N, =5<0T.
><1V=0FVO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8: 1C2 ?@>2545=89 @04 4>A;V465=L 7
;;>?V4>3@5;5< B0 V=H8<8 ?@5?0@0B0<8 4;O 282G5==O ?>B5=FV9=8E D0@<0:>48=0
0B5=>;>;><, =VD548?V=>< 01> 7 >1><0 ?@5?0@0B0<8 =5 1C;> 28O2;5=> ;;V=VG=>
7=0GCI>W D0@<0:>48=0W 270T<>4VW;
D5=>10@1VB0;>< B0 5AB@>35=0<8 =5 28O2;5=> 7=0G=>3> 2?;82C =0 D0@<0:>48=0
?V4>3@5;N;
483>:A8=>< 01> B5>DV;V=>D0@<0:>:V=5B8G=V ?>:07=8:8 =5 7
0=B0F84=8<8 70A>10<8: 2?;82C =0 @V25=L 01A>@1FVW ;;>?V4>3@5;N =5 28O2;5=>;
D5=VB>W=>< V B>;1CB0 :0@1>:A8;L=V <5B01>;VB8 ;;>?V4>3@5;N <>6CBL
?@83=VGC20B8 0:B82=VABL F8B>E@><>65 ?>B5=FV9=> ?V428IC20B8 @V2=V 2 ?;072V
B0:8E ;V:0@AL:8E 70A>1V2 O: D5=VB>W=, B>;1CB0 B0, O:V <5B01>;V7CNBLAO 450 2!9.
;5 =572060NG8 =0 F5, D5=VB>W= V B>;1CB0
4VC@5B8:0<8, β-04@5=>1;>:0B>@0<8, V=3V1VB>@0<8 0=3V>B5=78=:>=25@BCNG>3>
D5@<5=BC, 0=B03>=VAB0<8 :0;LFFN, 70A>10<8, I> 7=86CNBL @V25=L E>;5AB5@8=C,
:>@>=0@=8<8 207>48;0B0B>@0<8, 0=B84V015B8G=8<8 70A>10<8 (2;;NGONG8 V=AC;V=),
?@>B85?V;5?B8G=8<8 70A>10<8, 3>@<>=>70N B5@0?VTN B0 0=B03>=VAB0<8 GPIIb/IIIa:
C ;;V=VG=8E 4>A;V465==OE =5 1C;> 28O2;5=> ;;V=VG=> 7=0GCI8E ?>1VG=8E 5D5:BV2.

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

\$0@<0:>48=0

;>?V4>3@5;L A5;5:B82=> V=3V1CT 72'O7C20==O 045=>78=48D>AD0BC (\$) 7 9>3>
@5F5?B>@0<8 =0 ?>25@E=V B@><1>F8BV2, 1;>:CT 0:B820FVN B@><1>F8BV2 V B0:8<
G8=>< ?@83=VGCT WE 03@530FVN. =3V1CT B0:>6 03@530FVN B@><1>F8BV2, O:0
A?@8G8=5=0 V=H8<8 03>=VAB0<8. 0;L<1>F8BV2 A?>AB5@V30TBLAO G5@57 2 3>48=8

?VA;O ?5@>@0;L=>3> ?@89>2>W 4>78 ?@5?0@0BC. @8 ?>2B>@=>AC20==V 5D5:B
?>A8;NTBLAO, 0 AB01V;L=89 AB0= 4>AO30TBLAO G5@57 3-7 4=V2 ;V:C20==O
(A5@54=V9 @V25=L 30;L28BL 40-60 %). 3@530FVO B@><1>F8BV2 V G0A :@>2>B5GV
?>25@B0NBLAO 4> ?>G0B:>2>3> @V2=O 2 A5@54=L>AC20==O ?@5?0@0BC 2V4?>2V4=>
4> 2V4=>2;5==O B@><1>F8BV2.

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

VA;O ?5@>@0;L=>3> ?@89>2A<>:BCTBLAO 7 H;C=:>2>.:8H:>2>3> B@0:BC.
>=F5=B@0FVO 9>3> 2 ?;072V =57=0G=0 V G5@57 2 3>48=8 ?VA;O 70AB>AC20==O =5
287=0G0TBLAO (<5=H5 0,025 1V>B@0=AD>@3> >A=>2=89 <5B01>;VB (85 %
F8@:C;NNG>W 2 ?;07;C:8) T =50:B82=8;L=89 <5B01>;VB H284:> B0 =572>@>B=L>
72'O7CTBLAO 7 @5F5?B>@0<8 B@><1>F8BV2. # ?;072V 2V= =5 28O2;OTBLAO.
;>?V4>3@5;L B0 >A=>2=89 F8@:C;NNG89 <5B01>;VB 72>@>B=L> 72'O7CNBLAO 7 1V;:0<8
?;07<8.

VA;O ?5@>@0;L=>3> ?@89>50 % ?@89=OB>W 4>78 284V;OTBLAO V7 A5G5N V 46 % 7 :0;>
< ?@>B03>< 120 3>48= ?VA;O 70AB>AC20==O. 5@V>4 =0?V2282545==O >A=>2=>3>
<5B01>;VBC AB0=>28BL 8 3>48=
>=F5=B@0FVO >A=>2=>3> <5B01>;VBC 2 ?;073> 2V:C (75 @>:V2 V AB0@H5) 7=0G=> 28I0,
>4=0: 1V;LH 28A>:V :=F5=B@0FVW 2 ?;072V =5 AC?@>2>46CNBLAO 7

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

A=>2=V DV78:>-EVABV: B01;5B:8 :@C3;>W D>@<8 7 42>>?C;:>N ?>25@E=5N, 2:@8BV
?;V2:>2>N >1>;>=:>N @>652>3> :>;L>@C.

"5@ABV. 2 @>:8.

#<>28 715@V30==O.

>@83V=0;L=V9 C?0:>2FV ?@8 B5
15@V30B8 2 =54>ABC?=>

#?0:>2:0.

> 10 B01;5B>: C 1;VAB5@V, ?> 1 1;VAB5@C 2 ?0GFV; ?> 10 B01;5B>: C 1;VAB5@V, ?> 3
1;VAB5@8 2 ?0GFV.

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

8@>1=8:.

C1;VG=5 0:FV>=5@=5 B>20@8AB2> «0C:>2>-28@>1=8G89 F5=B@ <>@I03V2AL:89 EV-D0@
<0F52B8G=89 702>4».

VAF57=0E>465==O.

#:@0W=0, 03134, <. 8W2, 2C;.: 8@C, 17.

!" #&/
?> <548F8=A:>

"
(ATROGREL)

!>AB02:

459AB2CNI55 25I5AB2> : ;>?84>3@5;;

1 B01;5B:0 A>45@68B ;;>?84>3@5; 2 2845 ;;>?84>3@5;0 18AC;LD0B0, 2 ?5@5AG5B5 =0 100 %
;>?84>3@5; - 75 <3;

2A?><>30B5;L=K5 25I5AB20: =0B@8O :@>A:0@<5;>70, F5;;N;>70 <8:@>:@8AB0;;8G5A:0O,
;0:B>7K <=>384@0B, <0A;> @8F8=>2>5 384@>35=878@>20=>5;

?;5=>G=0O >I>;>G:0: 384@>:A8?@>?8;<5B8;F5;;N;>70, ;0:B>7K <=>384@0B, B8B0=0
48>:A84 (171), B@80F5B8=, :0@<8= (120).

5:0@AB25==0O D>@<0. "01;5B:8, ?>:@KBK5 ?;5=>G=>9 >1>;>G:>9.

\$0@<0:>B5@0?52B8G5A:0O 3@C??0. □=B8B@><1>B8G5A:85 A@54AB20. >4 " ! 01!04.

;8=8G5A:85 E0@0:B5@8AB8:8.

>:070=8O.

@>D8;0:B8:0 ?@>O2;5=89 0B5@>B@><1>70:

□ C 1>;L=KE, :>B>@K5 ?5@5=5A;8 8=D0@:B <8>:0@40 (=0G0;> ;5G5=8O G5@57 =5A;>;L:>
4=59, => =5 ?>765 G5< G5@57 35 4=59 ?>A;5 2>7=8:=>25=8O), 8H5<8G5A:89 8=AC;LB
(=0G0;> ;5G5=8O G5@57 7 4=59, => =5 ?>765 G5< G5@57 6 <5AOF52 ?>A;5 2>7=8:=>25=8O),
8;8 C :>B>@KE 4803=>AB8@>20=> 701>;520=85 ?5@8D5@8G5A:8E 0@B5@89;

□ C 1>;L=KE A >AB@K< :>@>=0@=K< A8=4@>>

A >AB@K< :>@>=0@=K< A8=4@>>< 157 ?>4J5<0 A53<5=B0 ST (=5AB018;L=0O
AB5=>:0@48O 8;8 8=D0@:B <8>:0@40 157 7C1F0 Q), 2 B>< G8A;5 C ?0F85=B>2, :>B>@K< 1K;
CAB0=>2;5= AB5=B 2 E>45 ?@>2545=8O G5@57:>6=>9 :>@>=0@=>9 0=38?;0AB8:8, 2 :>
<18=0F88 A 0F5B8;A0;8F8;>2>9 :8A;>B>9;

A >AB@K< 8=D0@:B>< <8>:0@40 A ?>4J5<< A53<5=B0 ST 2 :><18=0F88 A
0F5B8;A0;8F8;>2>9 :8A;>B>9 (C 1>;L=KE, :>B>@K5 ?>;CG0NB AB0=40@B=>5 <548:0
<5=B>7=>5 ;5G5=85 8 :>B>@K< ?>:070=0 B@><1>;8B8G5A:0O B5@0?8O).

@>D8;0:B8:0 0B5@>B@><1>B8G5A:8E 8 B@><1>M<1>;8G5A:8E A>1KB89 ?@8
D81@8;;OF88 ?@54A5@489.

;;>?84>3@5; ?>:070= 2 :><18=0F88 A 0F5B8;A0;8F8;>2>9 :8A;>B>9 27@>A;K< ?0F85=B0< A
D81@8;;OF85 ?@54A5@489, C :>B>@KE ACI5AB2C5B: ?> <5=LH59 <5@5 >48= D0:B>@
@8A:0 2>7=8:=>25=8O A>AC48ABKE A>1KB89; ?@>B82?>:070=85 : ;5G5=8N 0=B03=>8AB0
<8 28B0<8=0 (); =87:89 @8A: 2>7=8:=>25=8O :@>2>B5G5=8O, 4;O ?@>D8;0:B8:8 0B5@>B@>
<1>B8G5A:8E 8 B@><1>M<1>;8G5A:8E A>1KB89, 2 B>< G8A;5 8=AC;LB0.

@>B82?>:070=8O.

□ >2KH5==0O GC2AB28B5;L=>ABL : 459AB2CNI5

□ BO65;0O ?5G5=>G=0O =54>AB0B>G=>ABL;

□ >AB@K5 :@>2>B5G5=8O (2 B>< G8A;5 2=CB@8G5@5?=K5 :@>2>87;8O=8O) 8

701>;520=8O, ?@54@0A?>;030NI85 : 8E @0728B8N (=0?@8<5@, O725==0O 1>;57=L 65;C4:0 8
425=04F0B8?5@AB=>9 :8H:8 2 AB0488 >1>AB@5=8O, =5A?5F8D8G5A:89 O725==K9 :>;8B).

!>A>1 ?@8<5=5=8O 8 4>7K.

7@>A;K5 8 ?0F85=BK ?>68;>3> 2>7@0AB0. @5?0@0B =07=0G0NB ?> 1 B01;5B:5 (75 <3) 1
@07 2 ACB:8 =57028A8<> >B ?@85<0 ?8I8.

?0F85=B>2 A>AB@K< :>@>=0@=K< A8=4@>>< 157 ?>4J5<0 A53<5=B0 ST

(=5AB018;L=0O AB5=>:0@48O 8;8 8=D0@:B <8>:0@40 157 7C1F0 Q =0 -) ;5G5=85

;>?84>3@5;> <=0G8=0NB A >4=>:@0B=>9 =03@C7>G=>9 4>7K 300<3, 0 70B5< ?@>4>;60NB
4>7>9 75 <3 1 @07 2 ACB:8 (A 0F5B8;A0;8F8;>2>9 :8A;>B>9 (!) 2 4>75 75-325<3 2 ACB:8).

>A;>;L:C ?@8<5=5=85 1>;55 2KA>:8E 4>7 !>?2KH05B @8A: :@>2>B5G5=8O, @5:>

<5=4C5BAO =5 ?@52KH0BL 4>7C !100 <3. ?B8<0;L=0O ?@>4>;68B5;L=>ABL ;5G5=8O D>@
<0;L=> =5 CAB0=>2;5=0. 57C;LB0BK 8AA;54>20=89 A2845B5;LAB2CNB 2 ?>;L7C ?@8

<5=5=8O ?@5?0@0B0 4> 12 <5AOF52, 0 <0:A8<0;L=K9 MDD5:B =01;N40;AO G5@57 3
<5AOF0 ;5G5=8O.

?0F85=B>2 A>AB@K< 8=D0@:B<< <8>:0@40 A ?>4J5<<< A53<5=B0 ST :;>?84>3@5;
=07=0G0NB ?> 75 <3 1 @07 2 ACB:8, =0G8=0O A >4=>:@0B=>9 =03@C7>G=>9 4>7K 300<3 2
:><18=0F88 A !, A ?@<8<5=5=85< B@><1>;8B8G5A:8E ?@5?0@0B>2 8;8 157 =8E. 5G5=85
?0F85=B>2 2 2>7@0AB5 AB0@H5 75 ;5B =0G8=0NB 157 =03@C7>G=>9 4>7K :;>?84>3@5;0. >
<18=8@>20==CN B5@0?8N A;54C5B =0G8=0BL :0: <6=> @0=LH5 ?>A;5 ?>O2;5=8O A8<>2 8
?@>4>;60BL ?> :@09=59 <5@5 G5BK@5 =545;8. >;L70 >B ?@8<5=5=8O :><18=0F88
:;>?84>3@5;0 A !A2KH5 4 =545;L ?@8 MB< 701>;520=88 =5 87CG0;0AL.
0F85=B0< A D81@8;;OF859 ?@54A5@489 :;>?84>3@5; ?@8<5=ONB 2 @07>2>9 ACB>G=>9
4>75 75 <3. <5AB5 A :;>?84>3@5;< A;54C5B =0G8=0BL ?@8<5=5=85 !(2 4>75 75-100 <3 2
ACB:8) 8 ?@>4>;60BL 53>.

A;CG05 ?@>?CA:0 4>7K:

5A;8 A <><5=B0, :>340 =C6=> 1K;> ?@8=OBL >G5@54=CN 4>7C, ?@>H;> <5=LH5 12 G0A>2
?0F85=B 4>;65= =5<54;5=> ?@8=OBL ?@>?CI5==CN 4>7C, 0 A;54CNICN 4>7C C65 ?@8=8
<0BL 2 >1KG=>5 2@5

5A;8 ?@>H;> 1>;55 12 G0A>2, ?0F85=B 4>;65= ?@8=8<0BL A;54CNICN 4>7C 2 >1KG=>5 2@5
7C A F5;LN :>20=8O ?@>?CI5==>9 4>7K.

\$0@<0:>35=5B8:0. 0A?@>AB@0=5==>ABL 0;;5;59 CYP2C19, :>B>@K5 2K7K20NB ?@>
<56CB>G=CN 8 A=865==CN <5B01>;8G5A:CN 0:B82=>ABL CYP2C19, >B;8G05BAO 2 7028A8
<>AB8 >B @0A>2>9/MB=8G5A:>9 ?@8=04;56=>AB8. ?B8<0;L=K9 @568< 4>78@>20=8O C ;8F
A >A;01;5==K< <5B01>;87<<< CYP2C19 ?>:0 5I5 =5 CAB0=>2;5=.

5B8. 57>?0A=>ABL 8 MDD5:B82=>ABL ?@8<5=5=8O ?@5?0@0B0 45BO< =5 CAB0=>2;5=K,
?>MB>5=OBL 45BO<.

>G5G=0O =54>AB0B>G=>ABL. "5@0?52B8G5A:89 >?KB ?@8<5=5=8O ?@5?0@0B0 ?0F85=B0
< A ?>G5G=>9 =54>AB0B>G=>ABLN >3@0=8G5= (A15==>AB8 ?@8<5=5=8O»).

5G5=>G=0O =54>AB0B>G=>ABL. "5@0?52B8G5A:89 >?KB ?@8<5=5=8O ?@5?0@0B0
?0F85=B0< A 701>;520=8O<8 ?5G5=8 A@54=59 BO65AB8 8 2>7<>6=>ABLN 2>7=8:=>25=8O 35
<>@@038G5A:>3> 480B570 >3@0=8G5= (A15==>AB8 ?@8<5=5=8O»).

>1>G=K5 @50:F88.

081>;55 @0A?@>AB@0=5==>9 ?>1>G=>9 @50:F859 1K;> :@>2>B5G5=85, :>B>@>5 G0I5
2A53> =01;N40;>AL 2 ?5@2K9 <5AOF ;5G5=8O.

@>2L 8 :8

- B@><1>F8B>?5=8O, ;59:>?5=8O, M>78=>D8;8O;
- =59B@>?5=8O, 2;;NG0O BO65;CN =59B@>?5=8N;
- B@><1>B8G5A:0O B@><1>F8B>?5=8G5A:0O ?C@?C@0 ("") (A15==>AB8 ?@8<5=5=8O»),
0?;0AB8G5A:0O 0=5<8O, ?0=F8B>?5=8O, 03@0=C;>F8B>7, BO65;0O B@><1>F8B>?5=8O,
3@0=C;>F8B>?5=8O, 0=5<8O, ?@8>1@5B5==0O 35<>D8;8O .

<

- AK2>@>B>G=>?>4>1=K9 A8=4@<, 0=0D8;0:B>84=K5/0=0D8;0:B8G5A:85 @50:F88;
- ?5@5:@5AB=0O 38?5@GC2AB28B5;L=>ABL <564C B85=>?8@848=0<8 (B0:8<8 :0:
B8:;>?848=, ?@0AC3@5;L) (A15==>AB8 ?@8<5=5=8O»).

A8E8G5A:85 =0@CH5=8O

- 30;;NF8=0F88, A?CB0==>ABL A>7=0=8O.

5@2=0O A8AB5<0

- 2=CB@8G5@5?>K5 :@>2>B5G5=8O (2 =5:>B>@KE A;CG0OE A ;5B0;L=K< 8AE>4<<),
3>;>2=0O 1>;L, ?0@5AB578O, 3>;>2>:@C65=85;
- 87<5=5=85 2:CA>2>3> 2>A?@8OB8O.

0B>;>38O >@30=>2 7@5=8O

- :@>2>B5G5=85 2 >1;0ABL 3;070 (:>=JN=:B820;L=>5, >:C;O@=>5, @5B8=0;L=>5).

0B>;>38O CE0 8 ;018@8=B0

- 25@B83>.

!>AC48ABK5 =0@CH5=8O

- 35<0B><0;

□ BO65;>5 :@>2>B5G5=85, :@>2>B5G5=85 87 >?5@0F8>==>9 @0=K, 20A:C;8B,
0@B5@80;L=00 38?>B5=78O.

5A?8@0B>@=K5, B>@0:0;L=K5 8 <5480AB8=0;L=K5 =0@CH5=8O

□ =>A>2>5 :@>2>B5G5=85;

□ :@>2>B5G5=8O 87 4KE0B5;L=KE ?CB59 (:@>2>E0@:0=L5, ;53>G=K5 :@>2>B5G5=8O),
1@>=E>A?07<, 8=B5@AB8F80;L=K9 ?=52<>=8B, M>78=>D8;L=00 ?=52<>=8O.

5;C4>G=>-.:8H5G=K5 =0@CH5=8O:

□ 65;C4>G=>-.:8H5G=K5 :@>2>B5G5=8O, 480@5O, 014<>8=0;L=00 1>;L, 48A?5?A8O;

□ O720 65;C4:0 8 425=04F0B8?5@AB=>9 :8H:8, 30AB@8B, @2>B0, B>H=>B0, 70?>@,
<5B5>@87<;

□ @5B@>?5@8B>=50;L=>5 :@>2>87;8O=85;

□ 65;C4>G=>-.:8H5G=K5 8 @5B@>?5@8B>=50;L=K5 :@>2>B5G5=8O A ;5B0;L=K< 8AE>4<<,
?0=:@50B8B, ;>;8B (2 G0AB=>AB8 O725==K9 8;8 ;8F8B0@=K9), AB<>0B8B.

5?0B>18;80@=0O A8AB5<0

□ >AB@0O ?5G5=>G=0O =54>AB0B>G=>ABL, 35?0B8B, 0=><0;L=K5 @57C;LB0BK

?>:070B5;59 DC=.F88 ?5G5=8.

>60 8 ?>4:>6=0O ::5BG0B:0

□ ?>4:>6=>5 :@>2>87;8O=85;

□ AK?L, 7C4, 2=CB@8:>6=K5 :@>2>87;8O=8O (?C@?C@0);

□ 1C;;57=K5 45@<0B8BK, B>:A8G5A:89 M?845@<0;L=K9 =5:@>;87, A8=4@< !B825=A0-
6>=A>=0, @<=0O M@8B5<0, 0=38>=52@>B8G5A:89 >B5.;, M@8B5<0B>7=0O AK?L,
:@0?82=8F0, <548:0<5=B>7=K9 A8=4@< 38?5@GC2AB28B5;L=>AB8, <548:0<5=B>7=>5
2KAK?0=85 A M>78=>D8;859 8 A8AB5<=K<8 ?@>O2;5=8O<8 (DRESS-A8=4@<), M:75<0,
?;>A:89 ;8H09.

>AB=>-8

□ -A:5;5B=K5 :@>2>87;8O=8O (35<0@B@>7), 0@B@8B, 0@B@0;38O, <80;38O.

>G:8 8 <>G52K45;8B5;L=0O A8AB5<0

□ 35<0BC@8O;

□ 3;><5@C;>=5D@8B, ?>2KH5=85 C@>2=O :@50B8=8=0 2 :@>28.

1I55 A>AB>O=85

□ ;8E>@04:0.

01>@0B>@=K5 8AA;54>20=8O

□ C4;8=5=85 2@5<5=8 :@>2>B5G5=8O, A=865=85 :>;8G5AB20 =59B@>D8;>2 8 B@>
<1>F8B>2.

5@54>78@>2:0.

!8 C25;8G5=85 2@5<5=8 :@>2>B5G5=8O A ?>A;54CNI8<8 >A;>6=5=8O<8.

5G5=85: A8<0B8G5A:>5. !?5F80;L=>3> 0=B84>B0 =5B. @8 =5>1E>48<>AB8 =5<54;5==>9

:>@>@5:F88 C4;8=82H53>AO 2@5<5=8 :@>2>B5G5=8O 459AB285 ;:>?84>3@5;0 <>6=>

CAB@0=8BL B@0=ADC7859 B@<1>F8B0@=>9 <0AAK.

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

7-70 >BACBAB28O ;:8=8G5A:8E 40==KE ?@8<5=5=8O ;:>?84>3@5;0 2 ?5@8>4 15@5

<5==>AB8 =5 @5:><5=4C5BAO =07=0G0BL ?@5?0@0B 15@5<5==K< 65=I8=0

58725AB=>, ?@>=8:05B ;8 ;:>?84>3@5; 2 3@C4=>5 <>;>:, ?>MB> 2@5< :>@<;5=85 3@C4LN
A;54C5B ?@5:@0B8BL.

5B8.

57>?0A=>ABL 8 MDD5:B82=>ABL ?@8<5=5=8O ;:>?84>3@5;O 45BO< =5 CAB0=>2;5=K,
?>MB>

A>15==>AB8 ?@8<5=5=8O.

@>2>B5G5=85 8 35<0B>;>38G5A:85 =0@CH5=8O.

7-70 @8A:0 @0728B8O :@>2>B5G5=8O 8 35<0B>;>38G5A:8E ?>1>G=KE @50:F89 A;54C5B =5

<54;5==> ?@>25AB8 @0725@=CBK9 0=0;87 :@>28 8/8;8 4@C385 A>>B25BAB2CNI85 B5ABK,

5A;8 2> 2@5 2>7<>6=>AB8 :@>2>B5G5=8O. 0: 8 4@C385 0=B8B@><1>F8B0@=K5
A@54AB20, :;>?84>3@5; A;54C5B A >AB>@>6=>ABLN ?@8<5=OBL ?0F85=B0< A ?>2KH5==K
< @8A:>< :@>2>B5G5=8O 2A;54AB285 B@023> 2<5H0B5;LAB20 8;8 4@C38E
?0B>;>38G5A:8E A>AB>O=89, 0 B0:65 2 A;CG05 ?@8<5=5=8O ?0F85=B0<8 0F5B8;A0;8F8;>2>9
:8A;>BK (!), 35?0@8=0, 8=3818B>@>2 3;8:>?@>B58=0 IIB/III0 8;8 =5AB5@>84=KE
?@>B82>2>A?0;8B5;L=KE ?@5?0@0B>2, 2 B>< G8A;5 8=3818B>@>2 &-2. 5>1E>48<> 2=8
<0B5;L=> A;548BL 70 ?@>O2;5=8O<8 C ?0F85=B>2 A8<>2 :@>2>B5G5=8O, 2 B>< G8A;5
A:@KB>3> :@>2>B5G5=8O, >A>15==> 2 ?5@2K5 =545;8 ;5G5=8O 8/8;8 ?>A;5 8=20782=KE
?@>F54C@ =0 A5@4F5 8 E8@C@38G5A:8E 2<5H0B5;LAB2. 4=>2@5<5==>5 ?@8<5=5=85
;>?84>3@5;0 A ?5@>@0;L=K<8 0=B8:>03C;O=B0<8 =5 @5:><5=4C5BAO, ?>A:>;L:C >= <>65B
CA8;8BL 8=B5=A82=>ABL :@>2>B5G5=89 (A 8 4@C385 284K 2708<>459AB289)).
A;CG05 ?;0=>2>3> E8@C@38G5A:>3> 2<5H0B5;LAB20, 5A;8 0=B8B@><1>B8G5A:89 MDD5:B
O2;O5BAO 2@5<5==> =565;0B5;L=K<, ;5G5=85 :;>?84>3@5;< A;54C5B ?@5:@0B8BL 70 7
4=59 4> >?5@0F88. 0F85=BK 4>;6=K A>>1I0BL 2@0G0< 8 AB<0B>;>30< > B><, GB> >=8
?@8=8<0NB :;>?84>3@5;; ?5@54 =07=0G5=85< 8< ;N1>9 >?5@0F88 8;8 ?5@54 ?@8<5=5=85<
=>2>3> ;5:0@AB25==>3> A@54AB20. :;>?84>3@5; C4;8=O5B ?@>4>;68B5;L=>ABL
:@>2>B5G5=8O, ?>MB> =C6=> >AB>@>6=> ?@8<5=OBL ?0F85=B0< A ?>2KH5==K< @8A:><
:@>2>B5G5=8O (>A>15==> 65;C4>G=>-.8H5G=>3> 8 2=CB@83;07=>3>).
0F85=B>2 A;54C5B ?@54C?@548BL, GB> 2> 2@5?84>3@5;<< (>B45;L=> 8;8 2 :<18=0F88 A !)
:@>2>B5G5=85 <>65B >AB0=02;820BLAO ?>765, G5<>1KG=>, GB> 8< =5>1E>48<> A>>1I0BL
2@0GC > :064<< A;CG05 =5>1KG=>3> (? ;>:0;870F88 8;8 ?@>4>;68B5;L=>AB8)
:@>2>B5G5=8O.
"@><1>B8G5A:0O B@><1>F8B>?5=8G5A:0O ?C@?C@0 (""").
G5=L @54:> =01;N40;8AL A;CG08 B@><1>B8G5A:>9 B@><1>F8B>?5=8G5A:>9 ?C@?C@K
("") ?>A;5 ?@8<5=5=8O :;>?84>3@5;0, 8=>340 4065 ?>A;5 53> :@0B:>2@5<5==>3> ?@8
<5=5=8O. ""?"@>O2;O5BAO B@><1>F8B>?5=859 8 <8:@>0=38>?0B8G5A:>9 35<>;8B8G5A:>9
0=5<859 A =52@>;>38G5A:8<8 ?@>O2;5=8O<8, 48ADC=:F859 ?>G5: 8;8 ;8E>@04:>9.
""O2;O5BAO ?>B5=F80;L=> ;5B0;L=K< A>AB>O=85<, B@51CNI8< =5<54;5==>3> ;5G5=8O, 2
G0AB=>AB8 ?;07<>D5@57>
@8>1@5B5==0O 35<>D8;8O.
!>>1I0;>AL > A;CG00E @0728B8O ?@8>1@5B5==>9 35<>D8;88 ?>A;5 ?@8<5=5=8O
;>?84>3@5;O. A;CG00E ?>4B25@645==>3> 87>;8@>20==>3> C25;8G5=8O
""(0:B828@>20==>3> G0AB8G=>3> B@><1>?;0AB8=>2>3> 2@5<5=8), GB> A>?@>2>6405BAO
8;8 =5 A>?@>2>6405BAO :@>2>B5G5=85<, 2>?@>A > 4803=>AB8@>20=88 ?@8>1@5B5==>9
35<>D8;88 4>;65= 1KBL @0AA<>B@5=. 0F85=BK A ?>4B25@645==K< 4803=>7><
?@8>1@5B5==>9 35<>D8;88 4>;6=K =0E>48BLAO ?>4 =01;N45=85< 2@0G0 8 ?>;CG0BL
;5G5=85, ?@8<5=5=85 :;>?84>3@5;O 4>;6=> 1KBL ?@5:@0I5=>.
5402=> ?5@5=5A5==K9 8H5<8G5A:89 8=AC;LB.
7-70 =54>AB0B>G=>AB8 40==KE =5 @5:><5=4C5BAO =07=0G0BL :;>?84>3@5; 2 ?5@2K5 7
4=59 ?>A;5 >AB@>3> 8H5<8G5A:>3> 8=AC;LB0.
&8B>E@>< 450 2 !19 (CYP2C19). \$0@<0:>35=5B8:0.
?0F85=B>2 A 35=5B8G5A:8 A=865==>9 DC=:F859 CYP2C19 =01;N405BAO<5=LH0O
:>=F5=B@0F8O 0:B82=>3> <5B01>;8B0 :;>?84>3@5;0 2 ?;07<5 :@>28 8 <5=55 2K@065==K9
0=B8B@><1>F8B0@=K9 MDD5:B, :@><5 B>3>, C =8E 7=0G8B5;L=> G0I5 2>7=8:0NB
A5@45G=>-A>AC48ABK5 >A;>6=5=8O ?>A;5 8=D0@:B0 <8>.0@40 ?> A@02=5=8N A
?0F85=B0<8 A =>@<0;L=K< DC=:F8=>8@>20=85< CYP2C19.
"0: :0 :;>?84>3@5;<5B01>;878@C5BAO 4> >1@07>20=8O A2>53> 0:B82=>3> <5B01>;8B0
G0AB8G=> ?>4 459AB285< CYP2C19, B> ?@8<5=5=85 ?@5?0@0B>2, A=860NI8E 0:B82=>ABL
MB>3> D5@<5=B0, 25@>OB=55 2A53>, ?@82545B : A=865=8N :>=F5=B@0F88 0:B82=>3>
<5B01>;8B0 :;>?84>3@5;0 2 ?;07<5 :@>28. "0: :0 :;>8=8G5A:>5 7=0G5=85 MB>3> 2708
<>459AB28O =5 2KOA=5=>, A;54C5B 871530BL >4=>2@5<5==>3> ?@8<5=5=8O ?@5?0@0B>2,
:>B>@K5 C3=5B0NB 0:B82=>ABL CYP2C19 (A
5@5:@5AB=0O @50:B82=>ABL <564C B85=>?8@848=0<8.
0F85=B>2 A;54C5B ?@>25@8BL =0 =0;8G85 2 0=0<=575 38?5@GC2AB28B5;L=>AB8 : 4@C38<
B85=>?8@848=0< (B0:8< :0: B8:;>?848=, ?@0AC3@5;L), ?>A:>;L:C ?>ABC?0;8 A>>1I5=8O >

?5@5:@5AB=>9 0;;5@388 <564C B85=>?8@848=0<8 (A1>G=K5 @50:F88»). @8<5=5=85
B85=>?8@848=>2 <>65B ?@825AB8 : 2>7=8=>25=8N >B ;53:8E 4> BO65;KE 0;;5@38G5A:8E
@50:F89, B0:8E :0: AK?L, >B5: 28=:5, 8;8 35<0B>;>38G5A:8E @50:F89, B0:8E :0: B@>
<1>F8B>?5=8O 8 =59B@>?5=8O. 0F85=BK, C :>B>@KE 2 ?@>H;>< 1K;8 2 0=0<=575
0;;5@38G5A:85 @50:F88 8/8;8 35<0B>;>38G5A:85 @50:F88 =0 >48= B85=>?8@848=, <>3CB 8
<5BL ?>2KH5==K9 @8A: @0728B8O B>9 65 8;8 4@C3>9 @50:F88 =0 4@C385
B85=>?8@848=K. 5:><5=4>20= <=>8B>@8=3 =0 =0;8G85 ?@87=0:>2
38?5@GC2AB28B5;L=>AB8 C ?0F85=B>2 A 0;;5@3859 =0 B85=>?8@848=K.
0@CH5=85 DC=:F88 ?>G5:.

"5@0?52B8G5A:89 >?KB ?@8<5=5=8O ;;>?84>3@5;0 ?0F85=B0< A ?>G5G=>9
=54>AB0B>G=>ABLN >3@0=8G5=, ?>MB>A>1 ?@8<5=5=8O 8 4>7K»).

0@CH5=85 DC=:F88 ?5G5=8.

?KB ?@8<5=5=8O ?@5?0@0B0 ?0F85=B0< A 701>;520=8O<8 ?5G5=8 A@54=59 BO65AB8 8 2>7
<>6=>ABLN 2>7=8=>25=8O 35<>@@038G5A:>3> 480B570 >3@0=8G5=. >MB>A>1 ?@8
<5=5=8O 8 4>7K»).

A?><>30B5;L=K5 25I5AB20.

@5?0@0B A>45@68B ;0:B>7C. 0F85=B0< A @54:>9 =0A;54AB25==>9 =5?5@5=>A8<>ABLN
30;0:B>7K, 45D8F8B>< ;0:B07K 0?0, =0@CH5=85<<0;L01A>@1F88 3;N:>7K-30;0:B>7K =5
A;54C5B ?@8<5=OBL 40==K9 ?@5?0@0B.

@5?0@0B A>45@68B <0A;> @8F8=>2>5 384@>35=878@>20==>5, :>B>@>5 <>65B 2K720BL
@0AAB@>9AB2> 65;C4:0 8 480@5N.

A;8 ?0F85=B 701K; ?@8=OBL 4>7C ?@5?0@0B0 8 ?@>H;> <5=55 12 G0A>2 ?>A;5 ?;0=>2>3>
?@85<0, B> ?@5?0@0B =5>1E>48<> ?@8=OBL :0: <>6=> 1KAB@55, ?>A;5 G53> A;54CNICN
4>7C A;54C5B ?@8=OBL 2>2@5H;> 1>;55 12 G0A>2 A;54C5B ?@>?CAB8BL ?@85<
701KB>9 4>7K 8 ?@8=OBL 2>2@57C ?@5?0@0B0. 54>?CAB8<> ?@8=8<0BL 42>9=CN 4>7C
?@5?0@0B0.

> 2@5<=5 A;54C5B ?@8=8<0BL 0;:>3>;L 87-70 ?>2KH5=8O @8A:0 65;C4>G=>.:8H5G=>3>
:@>2>B5G5=8O.

A>1K5 ?@54>AB5@565=8O >B=>A8B5;L=> C40;5=8O >AB0B:>2 8 >BE>4>2.

N1>9 =58A?>;L7>20==K9 ?@5?0@0B 8;8 >BE>4K =C6=> C=8GB>68BL 2 A>>B25BAB288 A
<5AB=K<8 B@51>20=8O<8.

!?!>A>1=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B< 8;8

@01>B5 A 4@C38<8 <5E0=87<0<8.

@5?0@0B =5 2;8O5B 8;8 >.07K205B =57=0G8B5;L=>5 2;8O=85 =0 A:>@>ABL @50:F88 ?@8
C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A 4@C38<8 <5E0=87<0<8 (A1>G=K5
@50:F88»).

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

5@>@0;L=K5 0=B8:>03C;O=BK: >4=>2@5<5==>5 ?@8<5=5=85 ;;>?84>3@5;0 A ?5@>@0;L=K
<8 0=B8:>03C;O=B0<8, 2 B>< G8A;5 A 20@D0@8=×, =5 @5:><5=4C5BAO, B0: :0: B0:0O :>
<18=0F8O <>65B CA8;8BL 8=B5=A82=>ABL :@>2>B5G5=89.

=3818B>@K 3;8:>?@>B58=0 Iib/IIIa. ;;>?84>3@5; A;54C5B A >AB>@>6=>ABLN =07=0G0BL
?0F85=B0< A ?>2KH5==K< @8A:>< :@>2>B5G5=8O 2A;54AB288 B@02<, >?5@0F89 8;8
4@C38E ?0B>;>38G5A:8E A>AB>O=89, ?@8 :>B>@KE >4=>2@5<5==> ?@8<5=ONB
8=3818B>@K 3;8:>?@>B58=0 Iib/IIIa.

F5B8;A0;8F8;>200 :8A;>B0 (!): 0F5B8;A0;8F8;>200 :8A;>B0 =5 87<5=O5B 8=3818@CNI53>
459AB28O ;;>?84>3@5;0 =0 \$-8=4CF8@C5<1>F8B>2, => ;;>?84>3@5; CA8;8205B 459AB285 !=0
03@530F8N B@><1>F8B>2, 8=4CF8@C5;;035=> A>2<5AB=> =0 ?@>BO65=88 ?5@8>40 4>
>4=>3> 3>40.

5?0@8=: 2 8AA;54>20=88, ?@>2545==>< A CG0AB85< 74>@>2KE 4>1@>2>;LF52, ?@8
<5=5=85 ;;>?84>3@5;0 =5 B@51>20;> 87<5=5=8O 4>7K 35?0@8=0 8 =5 87<5=O;> 2;8O=8O
35?0@8=0 =0 :>03C;0F8N. 4=>2@5<5==>5 ?@8<5=5=85 35?0@8=0 =5 87<5=O;>

8=3818@CNI53> 459AB28O ;;>?84>3@5;0 =0 03@530F8N B@<<1>F8B>2. >A>;L:C 2>7<>6=>
D0@<0:>48=0<8G5A:>5 2708<>459AB285 <564C ;;>?84>3@5;< 8 35?0@8=<< A ?>2KH5=85<
<@8A:0 :@>2>B5G5=8O, >4=>2@5<5=>5 ?@8<5=5=85 MB8E ?@5?0@0B>2 B@51C5B
>AB>@>6=>AB8.

"@><1>;8B8G5A:85 A@54AB20: 157>?0A=>ABL A>?CBAB2CNI53> ?@8<5=5=8O
;>?84>3@5;0, D81@8=A?5F8D8G5A:8E 8;8 D81@8==5A?5F8D8G5A:8E B@<<1>;8B8G5A:8E
A@54AB2 8 35?0@8=0 >F5=820;8 ?@8 CG0AB88 ?0F85=B>2 A >AB@K< 8=D0@:B<
<8>:0@40. '0AB>B0 ?>O2;5=8O ;;>8=8G5A:8 7=0G8<>3> :@>2>B5G5=8O 1K;0 ?>4>1=>9
G0AB>B5 ?>O2;5=8O, :>B>@00 =01;N40;0AL ?@8 A>?CBAB2CNI5< ?@85<5 B@>
<1>;8B8G5A:8E A@54AB2 8 35?0@8=0 A A!

5AB5@>84=K5 ?@>B82>2>A?0;8B5;L=K5 ?@5?0@0BK () : 2 8AA;54>20=88, ?@>2545=>< =0
74>@>2KE 4>1@>2>;LF0E, >4=>2@5<5=>5 ?@8<5=5=85 ;;>?84>3@5;0 8 =0?@>:A5=0
C25;8G820;> :;>8G5AB2> A:@KBKE 65;C4>G=>-.8H5G=KE :@>2>B5G5=89. 4=0:> 2284C
>BACBAB28O 8AA;54>20=89 >B=>A8B5;L=> 2708<>459AB28O ?@5?0@0B0 A 4@C38<8 4>
=0AB>OI53> 2@5<5=8 =5 2KOA=5=>, 2>7@0AB05B ;8 @8A: 65;C4>G=>-.8H5G=>3>
:@>2>B5G5=8O ?@8 ?@8<5=5=88 ;;>?84>3@5;0 A 4@C38<8 . >MB>1E>48<0 >AB>@>6=>ABL
?@8 >4=>2@5<5=>< ?@8<5=5=88 , 2 B>< G8A;5 8=3818B>@>2 &-2, A ;;>?84>3@5;>
4=>2@5<5=>5 ?@8<5=5=85 4@C38E ?@5?0@0B>2: B0: :0 ;;>?84>3@5;
<5B01>;878@C5BAO 4> >1@07>20=8O A2>53> 0:B82=>3> <5B01>;8B0 G0AB8G=> ?>4
459AB285< CYP2C19, B> 8A?;>;L7>20=85 ?@5?0@0B>2, A=860NI8E 0:B82=>ABL MB>3> D5@
<5=B0, 25@>OB=55 2A53>, ?@82545B : A=865=8N :>=F5=B@0F88 0:B82=>3> <5B01>;8B0
;>?84>3@5;0 2 ?;07<5 :@>28. ;8=8G5A:>5 7=0G5=85 MB>3> 2708<>459AB28O =5 2KOA=5=>, ?>
MB>4=>2@5<5=>3> ?@8<5=5=8O ?@5?0@0B>2, :>B>@K5 C3=5B0NB 0:B82=>ABL
CYP2C19.

?@5?0@0B0<, C3=5B0NI8< 0:B82=>ABL CYP2C19, >B=>AOBAO ><5?@07>;, M7>
<5?@07>;, D;C2>:A0<8=, D;C>:A5B8=, <>;>15<84, 2>@8:>=07>;, D;C:>=07>;,
B8;>;?848=, F8?@>D;>:A0F8=, F8<5B848=, :0@10<075?8=, >:A:0@1075?8= 8 E;>@0;.
=3818B>@K ?@>B>=>9 ?>MDD5:B82=>ABL 0=B8B@><1>B8G5A:>3> 459AB28O
;>?84>3@5;0 <>65B A=860BLAO ?>GB8 =0?>;>28=C ?@8 :><18=0F88 A . %>BO AB5?5=L
C3=5B5=8O 0:B82=>AB8 CYP2C19 ?>4 459AB285< @07=KE ?@5?0@0B>2, ?@8=04;560I8E :
;0AAC, =5 O2;O5BAO >48=0:>2>9, 8AA;54>20=8O C:07K20NB =0 ACI5AB2>20=85 2708
<>459AB28O ?@0:B8G5A:8 A> 2A5<8 ?@54AB028B5;O<8 40=>=>3> ;:0AA0. @8 MB><
@07156=>ABL ?@8<5=5=8O 2> 2@5<5=8 =5 2;8O5B =0 A=865=85 MDD5:B82=>AB8
;>?84>3@5;0. >MB>4=>2@5<5=>3> ?@8<5=5=8O, 70 8A.;NG5=85< A;CG052, :>340 MB>
O2;O5BAO 01A>;NB=> =5>IE>48
>:070B5;LAB2 B>3>, GB> 4@C385 ?@5?0@0BK, :>B>@K5 C<5=LH0NB ?@>4C:F8N :8A;>BK
2 65;C4:5, =0?@8<5@ 2-1;>:0B>@K (:@><5 F8<5B848=0, :>B>@K9 C3=5B05B 0:B82=>ABL
CYP2C19) 8;8 0=B0F84K, 2;8ONB =0 0=B8B@><1>F8B0@=CN 0:B82=>ABL ;;>?84>3@5;0,
=5B.

><18=0F8O A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8: 1K; ?@>2545= @O4 8AA;54>20=89
A ;;>?84>3@5;< 8 4@C38<8 ?@5?0@0B0<8 4;O 87CG5=8O ?>B5=F80;L=KE D0@<0:>48=0
<8G5A:8E 8 D0@<0:>:8=5B8G5A:8E 2708<>459AB289, :>B>@K5 ?>:070;8, GB> ?@8 ?@8
<5=5=88 ;;>?84>3@5;0 A:

0B5=>;>;><, =8D548?8=>< 8;8 A >1>8<8 ?@5?0@0B0<8 =5 1K;> 2KO2;5=> ;8=8G5A:8 7=0G8
<>3> D0@<0:>48=0<8G5A:>3> 2708<>459AB28O;

D5=>10@18B0;>< 8 MAB@>35=0<8 =5 2KO2;5=> ACI5AB25=>=>3> 2;8O=8O =0 D0@
<0:>48=0<8:C ;;>?84>3@5;0;

483>:A8=>< 8;8 B5>D8;;8=> D0@<0:>:8=5B8G5A:85 ?>:070B5;8 =5 87<5=O;8AL;

0=B0F84=K<8 A@54AB20<8: 2;8O=8O =0 C@>25=L 01A>@1F88 ;;>?84>3@5;0 =5 2KO2;5=>;

D5=8B>8=>< 8 B>;1CB0<84> :0@1>:A8;L=K5 <5B01>;8BK ;;>?84>3@5;0 <>3CB C3=5B0BL
0:B82=>ABL F8B>E@><0 450 2C9, GB> <>65B ?>B5=F80;L=> ?>2KH0BL C@>2=8 2 ?;07<5

:@>28 B0:8E ;5:0@AB25==KE A@54AB2 :0: D5=8B>8=, B>;1CB0<84 8 , :>B>@K5

<5B01>;878@CNBAO 450 2C9. > =5A<>B@O =0 MB>, D5=8B>8= 8 B>;1CB0<84 <>6=>

157>?0A=> ?@8<5=OBL >4=>2@5<5=> A ;;>?84>3@5;<;

- 48C@5B8:0<8, β-04@5=>1;>:0B>@0<8, 8=3818B>@0<8 0=38>B5=78=?@52@0I0NI53>

D5@<5=B0, 0=B03>=8AB0<8 :0;LF8O, A@54AB20<8, A=860NI8<8 C@>25=L E>;5AB5@8=0,
:>@>=0@=K<8 207>48;0B0B>@0<8, 0=B848015B8G5A:8<8 A@54AB20<8 (2 B>< G8A;5
8=AC;8=><), ?@>B82>M?8;5?B8G5A:8<8 A@54AB20<8, 3>@<>=>70<5AB8B5;L=>9
B5@0?859 8 0=B03>=8AB0<8 GPIIb/IIIa: 2 :;8=8G5A:8E 8AA;54>20=8OE =5 1K;> 2KO2;5=>
;8=8G5A:8 7=0G81>G=KE MDD5:B>2.

\$0@<0:>;>38G5A:85 A2>9AB20.

\$0@<0:>48=0<8:0.

;?84>3@5; A5;5:B82=> 8=3818@C5B A2O7K20=85 045=>78=48D>AD0B0 (\$) A 53>
@5F5?B>@0<8 =0 ?>25@E=>AB8 B@><1>F8B>2, 1;>:8@C5B 0:B820F8N B@><1>F8B>2 8 B0:8
<>1@07>< C3=5B05B 8E 03@530F8N. =3818@C5B B0:65 03@530F8N B@><1>F8B>2,
2K720==CN 4@C38<8 03>=8AB0<8. ">@<>65=85 03@530F88 B@><1>F8B>2 =01;N405BAO
G5@57 2 G0A0 ?>A;5 ?5@>@0;L=>3> ?@85<0 @07>2>9 4>7K ?@5?0@0B0. @8 ?>2B>@=><
?@8<5=5=88 MDD5:B CA8;8205BAO, 0 AB018;L=>5 A>AB>O=85 4>AB8305BAO G5@57 3-7
4=59 ;5G5=8O (A@54=89 C@>25=L B>@<>65=8O 03@530F88 A>AB02;O5B 40-60 %).
3@530F8O B@><1>F8B>2 8 2@52>B5G5=8O 2>72@0I0NBAO : 8AE>4=>2=N 2 A@54=5<
G5@57 7 4=59 ?>A;5 ?@5:@0I5=8O ?@8<5=5=8O ?@5?0@0B0 ?> <5@5 >1=>2;5=8O B@>
<1>F8B>2.

\$0@<0:>:8=5B8:0.

>A;5 ?5@>@0;L=>3> ?@85<0 ?@5?0@0B 1KAB@> 2A0AK205BAO 87 65;C4>G=>.:8H5G=>3>
B@0:B0. >=F5=B@0F8O 53> 2 ?;07<5 :@>28 =57=0G8B5;L=0O 8 G5@57 2 G0A0 ?>A;5 ?@8
<5=5=8O =5 >?@545;O5BAO (<5=55 0,025 18>B@0=AD>@<8@C5BAO 2 ?5G5=8. 3>
>A=>2=>9 <5B01>;8B (85 % F8@:C;8@CNI53> 2 ?;07<5 A>548=5=8O) O2;O5BAO =50:B82=K
;L=K9 <5B01>;8B 1KAB@> 8 =5>1@0B8<> A2O7K205BAO A @5F5?B>@0<8 B@><1>F8B>2.
?;07<5 :@>28 >= =5 >1=0@C68205BAO. ;?84>3@5; 8 >A=>2=>9 F8@:C;8@CNI89 <5B01>;8B
>1@0B8<> A2O7K20NBAO A 15;:0<8 ?;07
>A;5 ?5@>@0;L=>3> ?@85<0 >:>;> 50 % ?@8=OB>9 4>7K 2K45;O5BAO A <>G>9 8 46 % A :0;>
< 2 B5G5=85 120 G0A>2 ?>A;5 ?@8<5=5=8O. 5@8>4 ?>;C2K2545=8O >A=>2=>3> <5B01>;8B0
A>AB02;O5B 8 G0A>2.
>=F5=B@0F8O >A=>2=>3> <5B01>;8B0 2 ?;07<5 C ?0F85=B>2 ?>68;>3> 2>7@0AB0 (75 ;5B 8
AB0@H5) 7=0G8B5;L=> 2KH5, >4=0:> 1>;55 2KA>:85 :>=F5=B@0F88 2 ?;07<5 :@>28 =5
A>?@>2>640NBAO 87<5=5=8O<8 2 03@530F88 B@><1>F8B>2 8 2@5<5=8 :@>2>B5G5=8O.

\$0@<0F52B8G5A:85 E0@0:B5@8AB8:8.

A=>2=K5 D878:>-E8<8G5A:85 A2>9AB20: B01;5B:8 :@C3;>9 D>@O:>2K?C:;>9
?>25@E=>ABLN, ?>:@KBK5 ?;5=>G=>9 >1>;>G:>9 @>7>2>3> F25B0.

!@>: 3>4=>AB8. 2 3>40.

#A;>28O E@0=5=8O.

>@838=0;L=>9 C?0:>2:5 ?@8 B5
%@0=8BL 2 =54>ABC?=>< 4;O 45B59 <5AB5.
#?0:>2:0.
> 10 B01;5B>: 2 1;8AB5@5, ?> 1 1;8AB5@C 2 ?0G:5; ?> 10 B01;5B>: 2 1;8AB5@5, ?> 3
1;8AB5@0 2 ?0G:5.

0B53>@8O >B?CA:0. > @5F5?BC.

@>872>48B5;L.

C1;8G=>5 0:F8=>5@=>5 >1I5AB2> «0CG=>.-?@>872>4AB25==K9 F5=B@ «>@I03>2A:89 E8
<8:>-D0@<0F52B8G5A:89 702>4».

5AB>=0E>645=85.

#: @08=0, 03134, 3. 852, C;. 8@0, 17.