

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

!@-&/  
(SIMVACOR-DARNITSA)

!::04:

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

1 B01;5B:0

4>?>28=8: 1CB8;3V4@>:AV0=V7>; (320), 0A:>@1V=>20 :8A;>B0, ;8<==0 :8A;>B0 <=>3V4@0B, :@>E  
<0;L ?@565;0B8=V7>20=89, ;0:B>70 <=>3V4@0B, F5;N;>70 :@8AB0;VG=0, :0;LFVN AB50@0B, o  
?04@09 II 85 F @>65289.

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

\$0@<0:>B5@0?52B8G=0 3@C?0.

V?>;V?V4518, <=>:>=5=B=V. =3V1VB>@8 ->@54C:B078.

>4 "% !1001.

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

>:070==O.

V?5@E>;5AB5@8=5

V:C20==O ?5@28==>W 3V?5@E>;5AB5@8=5 7W 48A;V?V45?>2=5==O 4> 4VTB8, :>;8 2V4?>2V4L =0  
4VTBC B0 V=HV =5<548:0<5=B>7=V 70A>18 ;V:C20==O (=0?@8::04 DV78G=V ?@028, 7=865==O <0A8  
BV;0) T =54>AB0B=L>N.

V:C20==O 3><>783>B=>W AV<59=>W 3V?5@E>;5AB5@8=5?>2=5==O 4> 4VTB8 B0 V=H>3>

;V?V4>7=86C20;L=>3> ;V:C20==O (=0?@8::04 0D5@57C ;V?V4V2 =87L:>W IV;L=>ABV) 01> O:I> B0:V  
<5B>48 ;V:C20==O =5 T =0;56=8<8.

!5@F52>-AC48==0 ?@>DV;0:B8:0

=865==O A5@F52>-AC48==>W A<5@B=>ABV B0 70E2>@N20=>ABV C ?0FVT=BV2 7 O2=>N  
0B5@>A::5@>B8G=>N A5@F52>-AC48==>N E2>@>1>N 01> FC:@>28< 4V015B<, 7 =>@<0;L=8<8 01>  
?V428I5=8<8 @V2=O<8 E>;5AB5@8=C, O: 4>40B:>20 B5@0?VO 4;O :>@5:FVW V=H8E D0:B>@V2  
@878:C B0 4> V=H>W :0@4V?>@>B5:B82=>W B5@0?VW (482. @>74V; «\$0@<0:>;>3VG=V  
2;0AB82>ABV. \$0@<0:>48=0

@>B8?>:070==O.

V?5@GCB;82VABL 4> A8<20AB8B8=C 01> 1C4L-O:>W A::04>2>W ?@5?0@0BC.

0E2>@N20==O ?5GV=:8 2 0:B82=V9 D07V 01> =57@>7C20B:8.

03VB=VABL B0 ?5@V>4 3>4C20==O 3@C44N (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

!C?CB=V9 ?@89>< ?>BC6=8E V=3V1VB>@V2 CYP3A4 (?@5?0@0BV2, I> 71V;LHCNBL AUC  
?@81;87=> 2 5 @07V2 01> 1V;LH5), B0:8E O: VB@0:>=07>;, :5B>:>=07>;, ?>A0:>=07>;, 2>@8:>=07>;,  
V=3V1VB>@8 -?@>B5078 (=0?@8::04 =5;DV=02V@), 1>F5?@52V@, B5;0?@52V@, 5@8B@>4>=.

!C?CB=V9 ?@89>< 3578;C, F8::>A?>@8=C 01> 40=07>;C.

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

V0?07>= 4>7C20==O ?@5?0@0BC 2V4 5 4> 80 <3 ?5@>@0;L=> 1 @07 =0 4>1C 225G5@V. V41V@ 4>78  
?@5?0@0BC 70 ?>B@518 A;V4 74V9A=N20B8 7 V=B5@20;0<8 =5 <5=H5 =V6 4 B86=V 4> <0:A8  
<0;L=>W 4>1>2>W 4>78 80 <3, I> ?@89<0TBLAO 1 @07 =0 4>1C 225G5@V. >70 80 <3 @5:>

<5=4CTBLAO BV;L:8 4;O ?0FVT=BV2 7 BO6:>N 3V?5@E>;5AB5@8=5:8< @878:>< A5@F52>-AC48==8E  
CA::04=5=L, O:V =5 4>AO3;8 FV;59 ;V:C20==O =86G8<8 4>70<8, B0 :>;8 >GV:CTBLAO, I> :>@8ABL  
?5@52060B8<5 ?>B5=V9=V @878:8 (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O», «\$0@<0:>48=0

V?5@E>;5AB5@8=5

0FVT=BC A;V4 ?@87=0G8B8 AB0=40@B=C E>;5AB5@8=>7=86C20;L=C 4VTBC, O:>W 2V= ?>28=5=  
4>B@8BO3>< CAL>3> :C@AC ;V:C20==O ?@5?0@0B>

28G09=> ?>G0B:>20 4>70 ?@5?0@0BC AB0=>28BL 10-20 <3 =0 4>1C, O:0 ?@89<0TBLAO >4=>@07>2>, 225G5@V. ;O ?0FVT=BV2, O:8< =5>1EV4=5 7=0G=5 (1V;LH5 O: =0 45 %) 7=865==O @V2=O %!-), ?>G0B:>20 4>70 <>65 AB0=>28B8 20-40 <3 1 @07 =0 4>1C 225G5@V. V41V@ 4>7 70 =5>1EV4=>ABV ?>B@V1=> 74V9A=N20B8 A?>A>1<, 28;:045=8< 28I5.

><>783>B=0 AV<59=0 3V?5@E>;5AB5@8=5

8E>4OG8 7 @57C;LB0BV2 :>=B@>;L>20=>3> ;V=VG=>3> 4>A;V465==O, @5:><5=4>20=0 ?>G0B:>20 4>70 ?@5?0@0BC - 40 <3 =0 4>1C >4=>@07>2> 225G5@V. !8<20:>@®-0@=8FO A;V4 70AB>A>2C20B8 O: 4>?>2=5==O 4> V=H>3>;V?V4>7=86C20;L=>3>;V:C20==O (=0?@8;:04 0D5@57 C)) 01> O:I> B0:5 ;V:C20==O =54>ABC?=5.

15@F52>-AC48==0 ?@>DV;0:B8:0

28G09=0 4>70 ?@5?0@0BC 4;O ?0FVT=BV2 7 28A>:8< @878:>< @>728B:C %! (C ?>T4=0==V 7 3V?5@;V?V45 157 =5W) AB0=>28BL 20-40 <3 =0 4>1C >4=>@07>2> 225G5@V. 548:0<5=B>7=C B5@0?VN <>6=0 ?>G0B8 >4=>G0A=> V7 4VTB>N B0 DV7:C;LBC@>N. V41V@ 4>7 70 =5>1EV4=>ABV ?>B@V1=> 74V9A=N20B8 A?>A>1<, 28;:045=8< 28I5.

1C?CB=O B5@0?VO

!8<20:>@®-0@=8FO 5D5:B82=89 O: <>=>B5@0?VO, 0 B0:>6 C :><1V=0FVW V7 A5:25AB@0=B0<8 6>2G=8E :8A;>B. >7C A;V4 ?@89<0B8 01> 70 > 2 3>48=8 4>, 01> G5@57 > 4 3>48=8 ?VA;O ?@89>2G=8E :8A;>B.

;O ?0FVT=BV2, O:V ?@89<0NBL ?@5?0@0B >4=>G0A=> 7 DV1@0B0<8, :@V< 3578;C (482. @>74V; <<@>B8?>:070==O)), 01> 7 D5=>DV1@0B<, 4>70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 10 <3/45=L. ;O ?0FVT=BV2, O:V >4=>G0A=> 7 !8<20:>@<®-0@=8FO ?@89<0NBL 040@>=, 0<;>48?V=, 25@0?0 01> 48;BV075<, 4>1>20 4>70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 20 <3 (482. @>74V;8 <<A>1;82>ABV 70AB>AC20==O), <<70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T <>4VW)).

>7C20==O ?@8 =8@:>2V9 =54>AB0B=>ABV

# ?0FVT=BV2 7 ?>N =8@:>2>N =54>AB0B=VABN =5<0T =5>1EV4=>ABV 77C20==O.

# ?0FVT=BV2 7 BO6:>N =8@:>2>N =54>AB0B=VABN (;V@5=A :@50B8=V=C <30<;/E2) A;V4 @5B5;L=> 72068B8 4>FV;L=VABL ?@87=0G5==O ?@5?0@0BC C 4>7V 10<3 =0 4>1C B0, O:I> B0:5 4>7C20==O 22060TBLAO =5>1EV4=8<, ?@5?0@0B A;V4 ?@87=0G0B8 7 >15@56=VABN.

0AB>AC20==O ;VB=V< ?0FVT=B0<

5<0T ?>B@518 2 :>@53C20==V 4>78.

0AB>AC20==O 4VBO< B0 ?V4;VB:0< (10-17 @>:V2)

;O 4VB59 B0 ?V4;VB:V2 (E;?>FV 2V:>2>W AB04VW "0==5@0 B0 AB0@HV B0 4V2G0B0, C O:8E, ?@8=09<=V >48= @V: ?@8ACB=V9 <5=AB@C0;L=89 F8;); 2V:> 10-17 @>:V2 7 35B5@>783>B=>N AV <59=>N 3V?5@E>;5AB5@8=5<5=4>20=0 728G09=0 ?>G0B:>20 4>70 AB0=>28BL 10 <3 1 @07 =0 4>1C 225G5@V. > ?>G0B:C ;V:C20==O A8<20AB0B8=>< 4VBO< B0 ?V4;VB:0< A;V4 ?@87=0G8B8 AB0=40@B=C E>;5AB5@8=>7=86C20;L=C 4VTBC, O:>W A;V4 4>B@8 5:><5=4>20=V 4>78 10-40 <3 =0 4>1C; <0:A8<0;L=0 @5:><5=4>20=0 4>70 AB0=>28BL 40 <3 =0 4>1C. >7C A;V4 ?V418@0B8 V=482V4C0;L=>, 73V4=> 7 <5B>N ;V:C20==O, 70 @5:><5=40FVO<8 ;V:C20==O 2 ?54V0B@VW (482. @>74V;8 <<A>1;82>ABV 70AB>AC20==O), <<\$0@<0:>48=078 A;V4 ?@>2>48B8 7 V=B5@20;0<8 2 4 B86=V 01> 1V;LH5.

>A2V4 70AB>AC20==O ?@5?0@0BC 4VBO< ?@5?C15@B0B=>3> 2V:C >1<565=89.

**>1VG=V @50:FVW.**

I>:C B@02=>3> B@0:BC: 48A?5?AVO (=C4>B0, 1;N20==O, 30AB@0;3VO, 1V;L C 682>BV, 70?>@ 01> 4V0@50, <5B5>@87<), 35?0B8B, E>;5AB0B8G=0 6>2BO=8FO, ?V428I5==O 0:B82=>ABV <<?5GV=:>28E>> B@0=A0W D>AD0B078, :@50B8=D>AD>:V=078; 4C65 @V4:> 3>AB@89 ?0=:@50B8B, ?5GV=:>20 =54>AB0B=VABL.

I>:C =5@2>2>W A8AB5<8 B0 >@30=V2 GCBB0: 0AB5=VO, 70?0<>@>G5==O, 3>;>2=89 1V;L, ?>@CH5==O ?0<OBV; ?>@CH5==O A=C, 2;:NG0NG8 157A>==O, =VG=V 60E8; 45?@5AVO, AC4>8, ?0@5AB57VW, ?5@8D5@8G=0 =52@>?0BVO, =5GVB:VABL 7>@>2>3> A?@89=OBBO, ?>@CH5==O A <0:>28E 2V4GCBBV2.

I>:C :VAB:>2>-<O7>2>W A8AB5<8: ?0BVO, 78B, ;V7 7 01> 157 3>AB@>W =8@:>2>W =54>AB0B=>ABV, B5=48=>?0BVO, V=>4V CA;:04=5=0 @>7@82>

;5@3VG=V B0 V?0B>;>3VG=V @50:FVW: H:V@=89 28A8?, :@>?82'O=:0, A25@1V6, 0;>?5FVO, 0=3V>=52@>B8G=89 =01@O:, 2>2G0:>?>4V1=89 A8=4@<, @52<0B8G=0 ?>;V<1>F8B>?5=VO, 5>78=>DV;VO, 71V;LH5==O (, 0@B@8B, 0@B@0;3VO, D>B>A5=A81V;V70FVO, ?@>?0A=8FO, 3V?5@5 2V 4> >1;8GGO, 7048H:0, 45@<0B>78B, 60@.

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

I>:C 48E0;L=>W A8AB5<8: V=B5@AB8FV0;L=5 70E2>@N20==O ;535=L.

I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: 5@5:B8;L=0 48ADC=:FVO.

030;L=V ?>@CH5==O: 0AB5=VO, A;01:VABL, =574C60==O.

=HV: 2V4GCBB0 A5@F518BBO.

@8 ?@89>2V4><;O;8 ?@> ?V428I5==O HbA1c B0 @V2=V2 3;N:>78 A8@>20B:8 2 AB0=V =0BI5.

# E>4V ?>AB<0@:5B8=3>2>3> ?5@V>4C 7@V4:0 1C;8 ?>2V4><;5==O ?@> ?>@CH5==O :>3=VB82=>W DC=:FVW (=0?@8:;04, ?>@CH5==O ?0<OBV, A?;CB0=VABL A2V4>>ABV), ?>2O70=V V7

70AB>AC20==O< AB0B8=V2, 2;;NG0NG8 A8<20AB0B8=. # FV;>7=8<8 B0 >1>@>B=8<8 ?VA;O

?@8?8=5==O ?@89> ?>G0B:C ?>O28 A8 @>:V2) B0 7=8:=5==O A8 3 B86=V) 1C2 @V7=8

C65 @V4:> A?>AB5@V30;8AO 28?04:8 V>?>A5@54:>20=>W =5:@>B87CNG>W ?0BVW (), 0CB>VW

?0BVW, ?>2O70=>W V7 70AB>AC20==O< AB0B8=V2. E0@0:B5@87CTBLAO A;01:VABN ?@>:A8

<0;L=8E <07V2 V ?V428I5==O< @V2=O :@50B8=:V=078 2 A8@>20BFV, O:V =5 7=8:0NBL =572060NG8

=0 ?@8?8=5==O ?@89>7=0:0<8 =0 1V>?AVW <07V2 157 7=0G=>3> 70?0;5==O, ?>;V?H5==O< ?@8

70AB>AC20==V V45?@5A82=8E 70A>1V2.

@8 ?@89>2V4><;O;8 ?@> B0:V 4>40B:>2V ?>1VG=V O28I0: @>7;048 A=C, 2;;NG0NG8 =VG=V :>H

<0@8; AB0B520 48ADC=:FVO; FC:@>289 4V015B (G0AB>B0 ?>O28 70;560B8<5 2V4 =0O2=>ABV 01>

2V4ACB=>ABV D0:B>@V2 @878:C (@V25=L 3;N:>78 :@>2V =0BI5 ≥ 5,6 <<>;L/;, V=45:A <0A8 BV;0 >

30 :3/<2, ?V428I5=89 @V25=L B@83;VF5@84V2, 0@B5@V0;L=0 3V?5@B5=7VO 2 0=0<=57V)).

**5@54>7C20==O.**

V4>7C20==O A8<20AB0B8=C, ?@8 FL>4=>3> 7 E2>@8E =5 2V47=0G5=> A?5F8DVG=8E A8>

=0A;V4:V2. 0:A8<0;L=0 ?@89=OB0 4>70 AB0=>28;0 3,6 3.

V:C20==O: A8<0B8G=5, A;V4 28:;8:0B8 1;N20==O, ?@><8B8 H;C=>;, ?@87=0G5==O 0:B82>20=>3>

2C3V;;O, =5>1EV4=89 :=B@>;L 68BBT28E DC=:FV9, DC=:FVW ?5GV=:8 B0 0:B82=>ABV \$;

A?5F8DVG=>3> 0=B84>BC =5 VA=CT, 35>4V0;V7 =55D5:B82=89.

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

@>B8?>:070=89 C ?5@V>4 203VB=>ABV, ?@8 70AB>AC20==V ?@5?0@0BC 3>4C20==O 48B8=8

3@C44N A;V4 ?@8?8=8B8.

57?5:0 70AB>AC20==O ?@5?0@0BC C 203VB=8E =5 2AB0=>2;5=0. 5 1C;> ?@>2545=> 6>4=8E

:>=B@>;L>20=8E ;;V=VG=8E 4>A;V465=L A8<20AB0B8=C 70 CG0ABN 203VB=8E. C;8 >B@8<0=V

@V4:VA=V ?>2V4><;5==O ?@> 2@>465=V 0=><0;VW ?VA;O 2=CB@VH=L<0B:>2>W 5:A?>78FVW

V=3V1VB>@V2 -oA-@54C:B078. 4=0:, 0=0;V7 ?@81;87=> 200 203VB=8E, 70 O:8<8 A?>AB5@V30;8

?@>A?5:B82=> V 2 O:8E ?@>BO3>< ?5@H>3> B@8<5AB@C 1C;0 5:A?>78FVO A8<20AB0B8=C 01>

V=H>3> ?>4V1=>3> V=3V1VB>@0 -oA-@54C:B078 ?>:0702, I> G0AB>B0 2@>465=8E 0=><0;V9 1C;0

A?V2AB028<>N 7 B0:>N 2 7030;L=V9 ?>?C;OFVW. "0:>W :V;L:>ABV A?>AB5@565=L 1C;>

AB0B8AB8G=> 4>AB0B=L> 4;O 28:;NG5==O 71V;LH5==O :V;L:>ABV 2@>465=8E 0=><0;V9 2 2,5 @078

B0 28I5 ?>@V2=O=> 7 G0AB>B>N 2 7030;L=V9 ?>?C;OFVW.

%>G0 =5<0T 6>4=>3> 4>:07C B>3>, I> G0AB>B0 ?>O28 2@>465=8E 0=><0;V9 C =0I04:V2 ?0FVT=BV2,

O:V ?@89<0;8 A8<20AB0B8= 01> V=H89 ?>4V1=89 V=3V1VB>@ -oA-@54C:B078, 2V4@V7=OTBLAO

2V4 BVTW, I> A?>AB5@V30TBLAO 2 7030;L=V9 ?>?C;OFVW, ;V:C20==O<0B5@V A8<20AB0B8=><

<>65 7=878B8 C ?;>40 @V25=L <520;>=0BC, O:89 T ?@5:C@A>@< 1V>A8=B57C E>;5AB5@8=C.

B5@>A:;5@>7 T E@>=VG=8< ?@>F5A><, V 70728G09 ?@8?8=5==O ?@89>7=86C20;L=8E 70A>1V2 ?V4

G0A 203VB=>ABV <0T =57=0G=> ??;820B8 =0 2V440;5=89 @878:;, ?>2O70=89 7 ?5@28==>N

3V?5@E>;5AB5@8=5ABV 01> 4>B8, 4>:8 =5 1C45 ?V4B25@465==O, I> 6V=:0 =5 203VB=0.

>4C20==O 3@C44N. 52V4><>, G8 284V;OTBLAO A8<20AB0B8= 01> 9>3> <5B01>;VB8 2 <>;>:

<0B5@V. A:V;L:8 7=0G=0 :V;L:VABL ;V:V2 284V;OTBLAO &0B5@8=AL:5 <>;>:, 0 B0:>6 G5@57

25;8:89 @878: A5@9>7=8E ?>1VG=8E @50:FV9, 6V=:0<, O:V ?@89<0NBL A8<20AB0B8=, A;V4 CB@8

<0B8AL 2V4 3>4C20==O 3@C44N.

**VB8.**

57?5:0 B0 5D5:B82=VABL A8<20AB0B8=C C ?V4;VB:V2 (E;>?G8:V2, 0 B0:>6 C 4V2G0B, 2 O:8E I>=09  
<5=H5 1 @V: O: ?>G0;8AO <5=AB@C0FVW) 2V:< 10-17 @>:V2 7 35B5@>783>B=>N AV<59=>N  
3V?5@;V?V45FV=N20;0AO 2 :>=B@>;L>20=>A;V465==V. @>DV;L ?>1VG=8E 5D5:BV2 C ?0FVT=BV2,  
O:V ?@89<0;8 A8<20AB0B8=, 1C2 ?>4V1=89 4> B0:>3> C ?0FVT=BV2, O:V ?@89<0;8 ?;0F51>.  
0AB>AC20==O 4>7 1V;LH5 40 <3 =5 4>A;V46C20;>AL C 40=>W 3@C?8 ?0FVT=BV2. # 4>A;V465=V =5  
1C;> 70DV:A>20=> 2?;82 A8<20AB0B8=C =0 @VAB B0 AB0B5289 @>728B>: ?V4;VB:V2, 0 B0:>6 =0  
B@820;VABL <5=AB@C0;L=>3> F8;;C C 4V2G0B>:. V2G0B0 <0NBL 1CB8 ?@>:>=AC;LB>20=V I>4>  
<5B>4V2 :>=B@0F5?FVW ?@8 70AB>AC20==V A8<20AB0B8=C.  
;O ?0FVT=BV2 2V:< 4> 18 @>:V2 5D5:B82=VABL B0 157?5:C =5 4>A;V46C20;8 ?@>BO3< ?5@V>4V2  
;V:C20==O B@820;VABN 4>2H5 48 B86=V2; 2V440;5=V 5D5:B8 =0 DV78G=89, @>7C>289 B0  
AB0B5289 @>728B>: =52V4>  
!8<20AB0B8= =5 4>A;V46C202AO C ?0FVT=BV2 <>;>4H5 10 @>:V2, 0 B0:>6 C 4V2G0B>:, 2 O:8E I5 =5  
?>G0;8AO <5=AB@C0FVW.

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

V>?0BVO/@014>;V7. !8<20AB0B8=, O: V V=HV V=3V1VB>@8 ->-@54C:B078, <65 A?@8G8=8B8  
?0BVN, I> ?@>O2;OTBLAO C 283;04V <O7>2>3> 1>;N, E2>@>1;82>3> AB0=C 01> 7030;L=>W  
A;01:>ABV B0 AC?@>2>46CTBLAO 7@>AB0==O< 0:B82=>ABV :@50B8=D>AD>:V=078 1V;LH =V6 C  
10 @07V2 28I5 25@E=L>W <56V =>@<8. V>?0BVO <65 ?@>O2;OB8AO C D>@;V7C, I> V=>4V  
AC?@>2>46CTBLAO 3>AB@>N =8@:>2>N =54>AB0B=VABN, >1C<>2;5=>N 3;>1V=C@VTN. 878:  
?0BVW 71V;LHCTBLAO 70 @0EC=>: ?V428I5==O V=3V1CNG>W 0:B82=>ABV I>4> ->-@54C:B078 C  
?;072V.

/: V C 28?04:C 7 V=H8<8 V=3V1VB>@0<8 ->-@54C:B078, @878: @>728B:C ?0BVW/@014>;V7C  
70;568BL 2V4 4>78 ?@5?0@0BC.  
878: ?>O28 ?0BVW 1V;LH89 C ?0FVT=BV2, O:V ?@89<0NBL 80 <3 A8<20AB0B8=C, ?>@V2=O=> 7 B0:8  
< C ?0FVT=BV2, O:V >B@8 107CNBLAO =0 AB0B8=V. ">7C A8<20AB0B8=C 80 <3 ?>B@V1=>  
70AB>A>2C20B8 BV;L:8 ?0FVT=B0< 7 BO6:>N 3V?5@E>;5AB5@8=5  
0E>48 4:O 7=865==O @878:C @>728B:C ?0BVW, A?@8G8=5=>W 270T<>4VTN 7 V=H8<8 ;V:0@AL:8<8  
70A>10<8.

878: @>728B:C ?0BVW B0 @014>;V7C 7=0G=> 71V;LHCTBLAO ?@8 AC?CB=L>AC20==V A8  
<20AB0B8=C 7 ?>BC6=8<8 V=3V1VB>@0<8 CYP3A4, B0:8<8 O: VB@0:>=07>;, :5B>:>=07>;,  
?>A0:>=07>;, 2>@8:>=07>;, 5@8B@>@8 -?@>B5078 (=0?@8;:04 =5;DV=02V@), 1>F5?@52V@,  
B5;0?@52V@, =5D07>4>=, 0 B0:>6 7 3578;<;, F8;;>A?@8=< B0 40=07>;>AC20==O F8E ;V:0@AL:8E  
70A>1V2 ?@>B8?>:070=>.

878: @>728B:C ?0BVW B0 @014>;V7C B0:>6 71V;LHCTBLAO ?@8 AC?CB=L>AC20==V 040@>=C, 0  
<;>48?V=C, 25@0?0 48;BV075?0BVW, 2;;NG0NG8 @014>;V7, <65 71V;LH8B8AO ?@8 AC?CB=L>  
AC20==V DC7848=>2>W :8A;>B8 7V AB0B8=0<8.

V4?>2V4=>, I>4> V=3V1VB>@V2 CYP3A4, 70AB>AC20==O A8<20AB0B8=C 7 VB@0:>=07>;<;,  
:5B>:>=07>;<;, ?>A0:>=07>;<;, 2>@8:>=07>;<;, V=3V1VB>@0<8 -?@>B5078 (=0?@8;:04 =5;DV=02V@>  
<), 1>F5?@52V@<;, B5;0?@52V@<;, 5@8B@<;, :;0@8B@<;, B5;VB@< B0 =5D07>4>=<<  
?@>B8?>:070=>. /:I> B5@0?VN ?>BC6=8<8 V=3V1VB>@0<8 CYP3A4 (?@5?0@0B0<8, I> 71V;LHCNBL  
AUC ?@81;87=> 2 5 @07V2 01> 1V;LH5) =5<>6;82> 2V4CYP3A4: D;C:>=07>;<;, 25@0?0<, 48;BV075<>  
!;V4 C=8:0B8 AC?CB=L>3> ?@89>2>3> A>:C B0 A8<20AB0B8=C.

0AB>AC20==O A8<20AB0B8=C 7 3578;< ?@>B8?>:070=>. '5@57 ?V428I5=89 @878: @>728B:C ?0BVW  
B0 @014>;V7C 4>70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 10 <3 =0 4>1C 4;O ?0FVT=BV2, O:V  
?@89<0NBL A8<20AB0B8= 7 V=H8<8 DV1@0B0<8, :@V< D5=>DV1@0BC. !;V4 7 >15@56=VABN  
?@87=0G0B8 D5=>DV1@0B 7 A8<20AB0B8=<<, >A:V;L:8 :>65= 7 F8E ?@5?0@0BV2 <>65 A?@8G8=8B8  
?0BVN, O:I> ?@89<0TBLAO >:@5<>.

!8<20AB0B8= =5 A;V4 ?@89<0B8 >4=>G0A=> 7 DC7848=>2>N :8A;>B>N. C;8 ?>2V4<<;5==O ?@>  
@014>;V7 (2;;NG0NG8 45:V;L:0 ;5B0;L=8E 28?04:V2) C ?0FVT=BV2, O:V ?@89<0;8 FN :<1V=0FVN.  
0FVT=B0<, 4;O O:8E 70AB>AC20==O A8AB5<=>W DC7848=>2>W :8A;>B8 T 68BBT2> 206;828<,  
;V:C20==O AB0B8=< A;V4 ?@8?8=8B8 =0 G0A ;V:C20==O DC7848=>2>N :8A;>B>N. 0FVT=BC A;V4  
?>@5:<5=4C20B8 =5309=> 725@=CB8AL 4>;V:0@O C @07V ?>O28 C =L>3> 1C4L-O:8E A8ABV 2  
<O70E, 1>;N 01> E2>@>1;82>ABV. "5@0?VN AB0B8=<< <>6=0 2V4=>28B8 G5@57 AV< 4=V2 ?VA;O

?@89>AB0==L>W 4>78 DC7848=>2>W :8A;>B8. # 28=OB:>28E 28?04:0E, :>;8 =5>1EV4=5  
4>23>B@820;5 A8AB5<=5 ;V:C20==O DC7848=>2>N :8A;>B>N, =0?@8:;04, 4;O ;V:C20==O BO6:8E  
V=D5:FV9, =5>1EV4=VABL AC?CB=L>3> ?@89>.@5<>  
<<1V=>20=>3> 70AB>AC20==O A8<20AB0B8=C 2 4>70E ?>=04 20 <3 =0 4>1C 7 040@>=><, 0<;>48?V=>  
<, 25@0?0< 01> 48;BV075<>< A;V4 C=8:0B8.  
0FVT=B8, O:V ?@89<0NBL V=HV ;V:0@AL:V 70A>18, <0@:>20=V O: B0:V, I><0NBL ?> 7 A8  
<20AB0B8=><, >A>1;82> 7 28A>:8<8 4>70<8 A8<20AB0B8=C, <>6CBL <0B8 ?V428I5=89 @878:  
@>728B:C ?0BVW. @8 AC?CB=L>@V2 CYP3A4, =0?@8:;04, 48;BV075<5=4CTBLAO <0:A8<0;L=0 4>70  
20 <3 A8<20AB0B8=C.  
V4:VA=V 28?04:8 ?0BVW/@014>;V7C 0A>FVN20;8AL V7 AC?CB=V< ?@89><< V=3V1VB>@V2 -oA-  
@54C:B078 B0 ;V?V4><>48DV:CNG8E 4>7 (≥ 1 3/4>1C) =V0F8=C (=V:>B8=>2>W :8A;>B8); :>65= 7 F8E  
?@5?0@0BV2 <>65 28:;8:0B8 ?0BVN, O:I> ?@89<0TBLAO >:@5<>.  
V:0@V, O:V @>73;O40NBL 20@V0=B :<1V=>20=>W B5@0?VW A8<20AB0B8=C 7 ;V?V4>  
<>48DV:CNG8<8 4>70<8 (≥ 1 3/4>1C) =V0F8=C 01> ?@5?0@0B0<8, I>;N 2 <O70E, E2>@>1;82>ABV 01>  
A;01:>ABV, 7:>@5<0 ?@>BO3>< ?5@H8E 78 1C4L-O:>3> 7 F8E ;V:0@AL:8E ?@5?0@0BV2.  
@>B>G=>3> 4>A;V465==O ;V=VG=8E @57C;LB0BV2 =570;56=>3> :>?0BVW C ?0FVT=BV2  
:8B09AL:>W =0FV>=0;L=>ABV, O:V ?@89<0;8 A8<20AB0B8= 40 <3 B0 =V:>B8=>2C :8A;>BC  
/;0@>?V?@0=B 2000 <3/40 <3. ">15@56=VABN ;V:C20B8 ?0FVT=BV2 :8B09AL:>W =0FV>=0;L=>ABV  
A8<20AB0B8=>< (7:>@5<0 4>70<8 40 <3 01> 28I5) AC?CB=L> 7 ;V?V4><>48DV:CNG8<8 4>70<8 (≥ 1 3  
/4>1C) =V0F8=C 01> ?@5?0@0B0<8, I> ?0BVW ?@8 ?@89>78, ?0FVT=B0< :8B09AL:>W  
=0FV>=0;L=>ABV =5 @5:><5=4CTBLAO 70AB>AC20==O 80 <3 A8<20AB0B8=C 7 ;V?V4>  
<>48DV:CNG8<8 4>70<8 (≥ 1 3/4>1C) =V0F8=C 01> ?@5?0@0B0<8, I> <>, G8 VA=CT ?V428I5=89 @878:  
?0BVW C V=H8E ?0FVT=BV2 07V9AL:>3> ?>E>465==O, O:V ?@89<0NBL A8<20AB0B8= AC?CB=L> 7  
;V?V4><>48DV:CNG8<8 4>70<8 (≥ 1 3/4>1C) =V0F8=C 01> ?@5?0@0B0<8, I>  
8. V25=L :@50B8=:V=078 =5 A;V4 28 70 =0O2=>ABV 1C4L-O:>W 9<>2V@=>W 0;LB5@=0B82=>W  
?@8G8=8 ?V428I5==O :@50B8=:V=078, >A:V;L:8 F5 CA:;04=NT B;C<0G5==O =0O2=8E 7=0G5=L. @8  
7=0G=>G0B:C (1V;LH5 =V6 5-:@0B=5 ?>@V2=O=> 7 25@E=L>N <565N =>@<8) @V2=V A;V4  
?>2B>@=> 28  
5@54 ;V:C20==O<. #AVE ?0FVT=BV2, I> ?>G8=0NBL B5@0?VN A8<20AB0B8=><, 0 B0:>6 ?0FVT=BV2,  
O:8< 1C;> 71V;LH5=> 4>7C A8<20AB0B8=C, ?>B@V1=> ?>?5@548B8 ?@> <>6;82VABL 28=8:=5==O  
?0BVW B0 =5>1EV4=VABL =5309=>3> 725@=5==O 4> ;V:0@O C @07V 28=8:=5==O 1C4L-O:8E  
<O7>28E 1>;59 =5OA=>3> E0@0:B5@C, E2>@>1;82>ABV C <O70E 01> <O7>2>W A;01:>ABV.  
!;V4 4>B@815@56=>ABV I>4> ?0FVT=BV2 V7 A?@8OB;828<8 D0:B>@0<8 @>728B:C @014>;V7C.  
<5B>N 2AB0=>2;5==O 2V4?>2V4=>3> ?>G0B:>2>3> 7=0G5==O @V25=L :@50B8=:V=078 A;V4 28  
?>G0B:C ;V:C20==O 2 B0:8E A8BC0FVOE: ;VB=V9 2V: (2V: ≥ 65 @>:V2); 6V=>G0 AB0BL; ?>@CH5==O  
DC=:FVW =8@>; =5:>=B@>;L>20=89 3V?>B8@5>7; =0O2=VABL 2 >A>18AB>AV<59=>  
# B0:8E A8BC0FVOE @878: ;V:C20==O A;V4 @>73;O40B8 2V4=>A=><>6;82>W :>@8ABV, B0:>6 @5:>  
<5=4CTBLAO ;V=VG=89 <>=VB>@8=3. /:I> @0=VH5 C ?0FVT=B0 1C;> ?>@CH5==O 7 1>:C <O7V2  
?@8 ?@89> AB0B8=C, ;V:C20==O V=H8< 70A>1>< FL>3> ;:0AC ?>B@V1=> ?>G8=0B8 7  
>15@56=VABN. @8 7=0G=>W <56V =>@<8) ;V:C20==O =5 A;V4 @>?>G8=0B8.  
V4 G0A ;V:C20==O. @8 28=8:=5==V 1>;N, A;01:>ABV 01> A?07< AB0B8=C, A;V4 28 28O2;5=>, I> FV  
@V2=V 70 2V4ACB=>ABV A5@9>7=8E DV78G=8E =020=B065=L 7=0G=> ?V428I5=V (1V;LH5 =V6 C 5  
@07V2 28I5 25@E=L>W <56V =>@<8), ;V:C20==O A;V4 ?@8?8=8B8. /:I> A8<8 7 1>:C <O7V2 T BO6:8<8  
B0 28:;8:0NBL I>45==89 48A:>@B, =02VBL O:I> @V2=V :@50B8=:V=078 <5=H5 =V6 C 5 @07V2 28I5  
25@E=L>W <56V =>@<8, B> A;V4 @>73;O=CB8 =5>1EV4=VABL ?@8?8=5==O ;V:C20==O. /:I>  
?V4>7@NTBLAO ?0BVO 7 1C4L-O:>W V=H>W ?@8G8=8, ;V:C20==O A;V4 ?@8?8=8B8.  
/:I> A8<8 7=8:;8 B0 @V2=V :@50B8=:V=078 ?>25@=C;8AL 4> =>@<8, A;V4 @>73;O=CB8 ?>2B>@=89  
?@89>< B>3> 6 AB0B8=C 01> 0;LB5@=0B82=>3> AB0B8=C C =87L:V9 4>7V B0 ?V4 @5B5;L=8<  
:>=B@>;5  
8I89 2V4A>B>: ?0BVW A?>AB5@V302AO C ?0FVT=BV2, O:8< 71V;LHC20;8 4>7C 4> 80 <3. 5:>  
<5=4>20=> ?@>2>48B8 ?5@V>48G=5 287=0G5==O @V2=O :@50B8=:V=078, >A:V;L:8 F5 4>?>>65  
28O28B8 AC1:;V=VG=V 28?04:8 ?0BVW.  
"5@0?VN A8<20AB0B8=>< ?>B@V1=> B82> ?@8?8=8B8 C ?0FVT=BV2 70 :V;L:0 4=V2 4> 28:>=0==O  
25;8:8E >?5@0B82=8E 2B@CG0=L, 0 B0:>6 ?VA;O <548G=8E 01> EV@C@3VG=8E 2B@CG0=L.  
?:82 =0 ?5GV=:C

# ;V=VG=8E 4>A;V465==OE C 45O:8E 4>@>A;8E ?0FVT=BV2, O:V >45@6C20;8 A8<20AB0B8=, 2V47=0G0;>AO ABV9:5 ?V428I5==O @V2=O ?5GV=:>28E D5@<5=BV2 (?>=04 3 @078 28I5 25@E=L>W <56V =>@<8). @8 2V4 ?>ABC?>2> 25@B0TBLAO 4> 28EV4=>3> @V2=O. V428I5==O @V2=O B@0=A0 2>46C20;>AO 6>2BO=8F5N 01> V=H>N ;V=VG=>N A8<0B8:>N. 0=V @50:FVW =5 ?>2'O70=V 7 3V?5@GCB;82VABN. 5O:V 7 ?0FVT=BV2<0;8 2V4E8;5==O ?>:07=8:V2 DC=:FVW ?5GV=:8 4> ?>G0B:C B5@0?VW A8<20AB0B8=>< B0/01> A?>6820;8 =04;8H:>2C :V;L:VABL 0;:>3>;N. 5@54 ?>G0B:>< ;V:C20==O, 0 ?>BV< 2V4?>2V4=> 4> ;V=VG=8E ?>:070=L, CAV< ?0FVT=B0< @5:> <5=4CTBLAO ?@>2>48B8 DC=:FV>=0;L=V ?5GV=:>2V ?@>18. 0FVT=B0<, C O:8E ?;0=CTBLAO ?V428I8B8 4>7C A8<20AB0B8=C 4> 80 <3 =0 4>1C, DC=:FV>=0;L=V ?5GV=:>2V ?@>18 20@B> ?@>2>48B8 4> ?>G0B:C B8B@0FVW, ?>BV< G5@57 3 AO3=5==O 4>78 80 <3 =0 4>1C, ?VA;O G>3> ?5@V>48G=> ?>2B>@N20B8 (=0?@8;:04, 1 @07 C ?V2@>:C) ?@>BO3<< CAL>3> ?5@H>3> @>:C ;V:C20==O. A>1;82C C203C 20@B> ?@84V;OB8 ?0FVT=B0<, C O:8E ?V428I5=89 @V25=L A8@>20B:>28E B@0=A0AB0T, >A>1;82> ?@8 ABV9:>W <56V =>@<8, ?@5?0@0B 20@B> 2V4 @8 ;V:C20==V A8<20AB0B8=><, O: V V=H8<8 3V?>;V?V45< ?VA;O ?>G0B:C ;V:C20==O, G0AB><0;8 <8=CI89 E0@0:B5@, =5 AC?@>2>46C20;8AO 1C4L-O:8<8 A8<0<8 B0 =5 28<030;8 A:0AC20==O B5@0?VW. @5?0@0B A;V4 70AB>A>2C20B8 7 >15@56=VABN ?0FVT=B0<, O:V 7;>26820NBL 0;:>3>;5 DB0;L<>:>3VG=5 >1AB565==O. 0 2V4ACB=>ABV 1C4L-O:>3> <548:0<5=B>7=>3> ;V:C20==O 71V;LH5==O ?>;IV ?< ?@>F5AC AB0@V==O. V4>3>4=V 40=V 4>23>B@820;8E ;V=VG=8E 28?@>1C20=L =5 2:07CNBL =0 VA=C20==O H:V4;82>3> 2?;82C A8<20AB0B8=C =0 :@8HB0;8: >:0 ;N48=8. 0AB>AC20==O 2>AV1 ?>E8;>3> 2V:C D5:B82=VABL 70AB>AC20==O A8<20AB0B8=C 4;O ;V:C20==O E2>@8E 2V:<< AB0@H5 65 @>:V2, O:V >B@83> ?V4 G0A :>=B@>;L>20=8E ;V=VG=8E 4>A;V465=L, I> >FV=N20;0AL 2V4=>A=> 7=865==O @V2=V2 7030;L=>3> E>;5AB5@8=C B0 E>;5AB5@8=C ), 28O2;O;0AL B0:>N 6, O: V 4;O ?>?C;OFVW 7030;>1V;LH5==O G0AB>B8 ?>1VG=8E 5D5:BV2, O:V 18 28O2;O;8AL ;V=VG=> 01> ;01>@0B>@=8<8 ?>:07=8:0<8, =5 2V4. @5?0@0B 7C. 0FVT=B8 7 @V4:VA=8<8 A?04:>28<8 @>7;040<8 =5?5@5=>A8<>ABV 30;0:B>78, ;0:B07=>W =54>AB0B=>ABV 0?0 01> A8=4@<<< 3;N:>7>-30;0:B>7=>W <0;L01A>@1FVW =5 ?>28==V ?@89<0B8 F59 ?@5?0@0B. =B5@AB8FV0;L=0 E2>@>10 ;535=L. @> 28?04:8 V=B5@AB8FV0;L=>W E2>@>18 ;535=L ?>2V4<<;O;8 ?@8 ?@89>V4?>2V4=V ?@>O28 <>6CBL 2;;NG0B8 48A?=>5, =5?@>4C:B82=89 :0H5;L B0 ?>3V@H5==O 7030;L=>3> AB0=C 74>@>2O (2B<<0, 2B@0B0 <0A8 BV;0 B0 30@OG:0). /:I> T ?V4>7@0, I> C ?0FVT=B0 @>728=C;0AL V=B5@AB8FV0;L=0 E2>@>10 ;535=L, B5@0?VN AB0B8=< A;V4 ?@8?8=8B8. &C:@>289 4V015B. 52=V 4>:078 2:07CNBL =0 B5, I> AB0B8=8 O: ;0A ?V428ICNBL @V25=L 3;N:>78 2 :@>2V B0 C 45O:8E ?0FVT=BV2 7 28A>8< @878:<< @>728B:C FC:@>2>3> 4V015BC 2 <091CB=L> <5=4CTBLAO @>7?>G8=0B8 ;V:C20==O FC:@>2>3> 4V015BC. 4=0: =04 B0:8< @878:<< ?5@52060T :>@8ABL 7=865==O AB0B8=0<8 AC48=>>3> @878:C, V B>28=5= 1CB8 ?@8G8=>N 4;O ?@8?8=5==O ;V:C20==O AB0B8=0<8. 0FVT=BV2 7 @878:<< (3;N:>70 =0B15 5,6-6,9 <<>;L/; V=45:A <0A8 BV;0 >30 :3/ <2, ?V428I5=V B@83;VF5@848, 0@B5@V0;L=0 3V?5@B5=7VO) ?>B@V1=> <>=VB>@C20B8 O: ;V=VG=>, B0: V 1V>EV 2V4?>2V4=> 4> =0FV>=0;L=8E =0AB0=>2.

**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.**

18<20AB0B8= =5 <0T 6>4=>3> 01> <0T =57=0G=89 2?;82 =0 740B=VABL :5@C20B8 02B<<1V;5< B0 V=H8<8 <5E0=VG=8<8 70A>10<8. 4=0: ?@8 :5@C20==V 02B<<1V;O<8 01> @>1>BV 7 V=H8<8 <5E0=VG=8<8 70A>10<8 A;V4 2@0EC20B8, I> ?@>BO3<< ?5@V>4C ?>AB<0@:5B8=3>2>3> 70AB>AC20==O 7@V4:0 =04E>48;8 ?>2V4><;5==O ?@> 70?0<>@>G5==O.

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

>A;V465==O 270T<>4VW ?@>2>48;8AL BV;L:8 70 CG0ABN 4>@>A;8E.

\$0@<0:>48=0

70T<>4VW 7 ;V?V4>7=86CNG8<8 ;V:0@AL:8<8 70A>10<8, O:V ?@8 ?@89>:@5<< <>6CBL A?@8G8=8B8 ?0BVN.

878: ?0BVW, 2;:NG0NG8 @014>;V7, ?V428ICTBLAO ?V4 G0A AC?CB=L>3> ?@89>78;>;, O:0  
?@872>48BL 4> ?V428I5==O @V2=O A8<20AB0B8=C 2 ?;074>:07V2 B>3>, I> @878: ?0BVW ?5@528ICT  
AC6=>3> >:@5<>3> ?@5?0@0BC. 5<0T 4>AB0B=VE 40=8E D0@<0:>=03;04C B0 D0@<0:>:V=5B8G=8E  
40=8E ?@> V=HV DV1@0B8. =>4V 28?04:8 ?0BVW/@014>;V7C 0A>FVN20;8AO 7 AC?CB=V< ?@89><>  
< A8<20AB0B8=C 7 ;V?V4><>48DV:CNG8<8 4>70<8 (≥ 1 3/4>1C) =V0F8=C.

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

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8, I> 0A>FVNTBLAO 7 ?V428I5=8< @878:>< ?0BVW/@014>  
>;V7C.

@5?0@0B8, 70AB>AC20==O O:8E ?@>B8?>:070=5 ?@8 ?@89>

?>BC6=V V=3V1VB>@8 CYP3A4, =0?@8::04: VB@0:>=07>;, :5B>:>=07>;, ?>A0:>=07>;, 2>@V:>=07>;,  
5@8B@>@8 -?@>B5078 (=0?@8::04 =5;DV=02V@), 1>F5?@52V@, B5;0?@52V@, =5D07>4>=,  
F8::>A?>@8=, 40=07>;, 3578;.

@5?0@0B8, ?@8 70AB>AC20==V O:8E =5 A;V4 ?5@528IC20B8 4>7C 10 <3 =0 4>1C A8<20AB0B8=C:  
V=HV DV1@0B8 (70 28=OB:>< D5=>DV1@0BC).

@5?0@0B8, ?@8 70AB>AC20==V O:8E =5 A;V4 ?5@528IC20B8 4>7C 20 <3 =0 4>1C A8<20AB0B8=C: 0  
40@>=, 0<;>48?V=, 25@0?0, 48;BV075<.

@5?0@0B8, ACBC20==O O:8E V7 A8<20AB0B8=>< =5 @5:><5=4>20=>: DC7848=>20 :8A;>B0.

?;82 V=H8E ;V:0@AL:8E 70A>1V2 =0 A8<20AB0B8=.

70T<>4VO 7 V=3V1VB>@0<8 CYP3A4. !8<20AB0B8= F5 AC1AB@0B F8B>E@>P450 3A4. >BC6=V  
V=3V1VB>@8 F8B>E@>P450 3A4 ?V428ICNBL @878: ?0BVW B0 @014>;V7C H;OE<< ?V428I5==O  
:>=F5=B@0FVW V=3V1CNG>W 0:B82=>ABV ->.@54C:B078 2 ?;072V ?V4 G0A B5@0?VW A8  
<20AB0B8=> B0:8E V=3V1VB>@V2 =0;560BL VB@0:>=07>;, :5B>:>=07>;, ?>A0:>=07>;, 2>@8:>=07>;,  
5@8B@>@8 -?@>B5078 (=0?@8::04, =5;DV=02V@), 1>F5?@52V@, B5;0?@52V@ B0 =5D07>4>=.  
!C?CB=V9 ?@89>< VB@0:>=07>;C ?@872V2 4> ?V428I5==O 1V;LH5 =V6 C 10 @07V2 5:A?>78FVW 4>  
A8<20AB0B8=>2>W :8A;>B8 (0:B82=>3> <5B01>;VBC 15B0-3V4@>:A8:8A;>B8). "5;VB@> 11-@07>2>3>  
?V428I5==O 5:A?>78FVW 4> A8<20AB0B8=>2>W :8A;>B8.

><1V=0FVO 7 VB@0:>=07>;>;, :5B>:>=07>;>;, ?>A0:>=07>;>;, 2>@8:>=07>;>;, V=3V1VB>@0<8 -

?@>B5078 (=0?@8::04, =5;DV=02V@><), 1>F5?@52V@><, B5;0?@52V@><, 5@8B@><, :;0@8B@><,  
B5;VB@>< B0 =5D07>4>=>< ?@>B8?>:070=0, 0 B0:>6 7 3578;>;, F8::>A?>@8=>< B0 40=07>;>

B5@0?VN ?>BC6=8<8 V=3V1VB>@0<8 CYP3A4 (?@5?0@0B0<8, I> 71V;LHCNBL AUC ?@81;87=> 2 5  
@07V2 01> 1V;LH5) =5<>6;82> 2V4CYP3A4: D;C:>=07>;>;, 25@0?0< 01> 48;BV075<>

\$.C:>=07>;. @V4:0 ?>2V4><;O;>AO ?@> 28?04:8 @014>;V7C, I> 0A>FVN202AO 7 AC?CB=V< ?@89><>  
< A8<20AB0B8=C B0 D;C:>=07>;>;C.

?>A?>@8=. 878: @>728B:C ?0BVW/@014>;V7C 7@>AB0T ?@8 ?>T4=0=>A?>@8=C 7 A8<20AB0B8=>  
<; B>AC20==O 7 F8::>A?>@8=>< ?@>B8?>:070=5. %>G0 <5E0=V7< 4VW =5?>2=VABN 7@>7C?@>45  
<>=AB@>20=>, I> F8::>A?>@8= 71V;LHCT AUC V=3V1VB>@V2 ->.@54C:B078. 1V;LH5==O AUC 4;O  
A8<20AB0B8=C 2V41C20TBLAO, =0A02> G5@57 ?@83=VG5==O CYP3A4.

0=07>;. 878: @>728B:C ?0BVW B0 @014>;V7C 7@>AB0T ?@8 ?>T4=0=>;C 7 A8<20AB0B8=><; B>  
AC20==O 7 40=07>;>< ?@>B8?>:070=5.

578;. □578; 71V;LHCT AUC A8<20AB0B8=>2>W :8A;>B8 2 1,9 @070, <>6;82>, G5@57 ?@83=VG5==O  
H;OEC 3;N:C@>=V70FVW. !C?CB=T 70AB>AC20==O 7 3578;>< ?@>B8?>:070=5.

\$C7848=>20 :8A;>B0. 878: ?0BVW, 2;:NG0NG8 @014>;V7, <>65 ?V428IC20B8AO ?V4 G0A

AC?CB=L>3> ?@89>5E0=V7< B0:>W 270T<>4VW (D0@<0:>48=0 D0@<0:>:V=5B8:0, 01> >18420  
<5E0=V7<8) =0 40=89 G0A =52V4><89. C;8 ?>2V4><;5==O ?@> @014>;V7 (2;:NG0NG8 ;5B0;L=V  
28?04:8) C ?0FVT=BV2, O:V ?@89<0;8 FN :><1V=0FVN. /:I> 22060TBLAO 70 =5>1EV4=5

70AB>AC20==O DC7848=>2>W :8A;>B8, ;V:C20==O A8<20AB0B8=>< A;V4 ?@8?8=8B8 =0 G0A  
;V:C20==O DC7848=>2>N :8A;>B>N.

40@>=. 878: ?0BVW B0 @014>;V7C ?V428ICTBLAO ?V4 G0A AC?CB=L>3> ?@89>40@>=>4V

::V=VG=>3> 4>A;V465==O ?@> ?0BVN ?>2V4><8;8 6 % ?0FVT=BV2, O:V ?@89<0;8 A8<20AB0B8=C  
4>7V 80 <3 B0 040@>=.">70 A8<20AB0B8=C =5 ?>28==O ?5@528IC20B8 20 <3 =0 4>1C 4;O ?0FVT=BV2,  
O:V ?@89<0NBL F59 ?@5?0@0B AC?CB=L> 7 040@>=>

;:>:0B>@8 :0;LFVT28E :0=0;V2.

5@0?0 878: ?0BVW B0 @014>;V7C ?V428ICTBLAO ?V4 G0A AC?CB=L>3> ?@89< ?@872V2 4> 2,3-  
@07>2>3> 71V;LH5==O 5:A?>78FVW 4> A8<20AB0B8=>2>W :8A;>B8, =0A02> G5@57 ?@83=VG5==O  
CYP3A4. ">70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 20 <3 =0 4>1C 4;O ?0FVT=BV2, O:V ?@89  
<0NBL F59 ?@5?0@0B AC?CB=L> 7 25@0?0  
8;BV075<. 878: ?0BVW B0 @014>;V7C ?V428ICTBLAO ?V4 G0A AC?CB=L>3> ?@89> G5@57  
?@83=VG5==O CYP3A4. ">70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 20 <3 =0 4>1C 4;O  
?0FVT=BV2, O:V ?@89<0NBL F59 ?@5?0@0B AC?CB=L> 7 48;BV075<>  
<;>48?V=. 0FVT=B8, O:V ?@89<0NBL 0<;>48?V= AC?CB=L> 7 A8<20AB0B8=><, <0NBL ?V428I5=89  
@878: @>728B:C ?0BVW. # E>4V D0@<0:>:V=5B8G=>3> 4>A;V465==O AC?CB=V9 ?@89< 7 0  
<;>48?V=>< ?@872V2 4> 1,6-@07>2>3> 71V;LH5==O 5:A?>78FVW 4> A8<20AB0B8=>2>W :8A;>B8. ">  
70 A8<20AB0B8=C =5 ?>28==0 ?5@528IC20B8 20 <3 =0 4>1C 4;O ?0FVT=BV2, O:V ?@89<0NBL F59  
?@5?0@0B AC?CB=L> 7 0<;>48?V=>  
>@8 CYP3A4. 0FVT=B8, O:V ?@89<0NBL V=HV ;V:0@AL:V 70A>18,<0@:>20=V O: B0:V, I><0NBL ?>  
CYP3A4, AC?CB=L> 7 A8<20AB0B8=><, >A>1;82> 7 28I8<8 4>70<8 A8<20AB0B8=C, <>6CBL <0B8  
?V428I5=89 @878: ?>O28 ?0BVW.  
V0F8= (=V:>B8=>20 :8A;>B0). V4:VA=V 28?04:8?0BVW/@014>;V7C 0A>FVN20;8AO 7 AC?CB=V<  
?@89><< 7 ;V?V4><>48DV:CNG8<8 4>70<8 (≥1 3/4>1C) =V0F8=C. # E>4V D0@<0:>:V=5B8G=>3>  
4>A;V465==O AC?CB=V9 ?@89< >4=>@07>2> 4>78 2 3 =V:>B8=>2>W :8A;>B8 ?@>;>=3>20=>W 4VW  
7 A8<20AB0B8=>< C 4>7V 20 <3 ?@872V2 4> ?>3> ?V428I5==O AUC A8<20AB0B8=C B0 A8  
<20AB0B8=>2>W :8A;>B8 B0 :=F5=B@0FV9 C<sub>max</sub> A8<20AB0B8=>2>W :8A;>B8 2 ?;07  
!V: 3@59?D@CB0. !V: 3@59?D@CB0 48= 01> 1V;LH5 :=5=BV2, O:V V=3V1CNBL CYP3A4 V <>6CBL  
?V428I8B8 :=F5=B@0FVN 2 ?;072V ?@5?0@0BV2, O:V <5B01>;V7CNBLAO ?V4 2?;82>< CYP3A4.  
1V;LH5==O 0:B82=>ABV V=3V1VB>@V2 ->-@54C:B078 ?VA;O AB0=40@B=>3> 26820==O 250<; A>:C  
=0 45=L T 2V V 28I5N ?V4 :@82>N «:=F5=B@0FVO-G0A») V =5 <0T ::V=VG=>3> 7=0G5==O. @>B5  
A?>6820==O 25;8:>3> >1T:C 7=0G=> ?V428ICT @V25=L V=3V1CNG>W 0:B82=>ABV 2V4=>A=> ->-  
@54C:B078 2 ?;072V, C 7207:C 7 F8< =5>1EV4=> C=8:0B8 26820==O A>:C 3@59?D@CB0 ?@8  
70AB>AC20==V A8<20AB0B8=C.  
>;EVF8=. C;8 ?>2V4><;5==O ?@> ?0BVN B0 @014>;V7 ?@8 AC?CB=L>;EVF8=C B0 A8<20AB0B8=C C  
?0FVT=BV2 7 =8@:>2>N =54>AB0B=VABN. 5:>5=4CTBLAO @5B5;L=89 ;V=VG=89 <>=VB>@8=3  
?0FVT=BV2, O:V ?@89<0NBL FN :><1V=0FVN.  
8D0 A:V;L:8 @8D0BC6=8< AB8@>< CYP3A4, C ?0FVT=BV2, O:V ?@>E>4OBL 4>23>B@820;C  
B5@0?VN @8D0<, <>6;820 2B@0B0 5D5:B82=>ABV A8<20AB0B8=C. # E>4V D0@<0:>:V=5B8G=>3>  
4>A;V465==O 70 CG0ABN 74>@>28E 4>1@>2>;LFV2 ?;>I0 ?V4 :@82>N «:=F5=B@0FVO-G0A») (AUC)  
4;O A8<20AB0B8=>2>W :8A;>B8 7<5=H8;0AL =0 93 % ?@8 AC?CB=L>  
?:82 A8<20AB0B8=C =0 D0@<0:>:V=5B8:C V=H8E ;V:0@AL:8E 70A>1V2  
18<20AB0B8= =5 <0T V=3V1CNG>3> 2?;82C =0 F8B>E@>< P450 3A4. ">GV:CNBL, I> A8<20AB0B8=  
2?;820B8<5 =0 :=F5=B@0FVW 2 ?;0728=, I> <5B01>;V7CNBLAO 70 CG0ABN F8B>E@>  
5@>@0;L=V 0=B8:>03C;O=B8. V4 G0A 42>E ;V=VG=8E 4>A;V465=L, >4=5 7 O:8E ?@>2>48;>AO 70  
CG0ABN 74>@>28E 4>1@>2>;LFV2, 0 V=H5 70 CG0ABN ?0FVT=BV2 7 3V?5@E>;5AB5@8=54=5 =>@>  
<0;V7>20=5 A?V22V4=>H5==O, 7@>AB02 C 74>@>28E 4>1@>2>;LFV2 2V4 28EV4=>3> ?>:07=8:0 1,7  
4> 1,8, 0 C ?0FVT=BV2 7 3V?5@E>;5AB5@8=5 3,4. C65 @V4:> ?>2V4><;O;8 ?@> ?V428I5==O 4=>3>  
=>@<0;V7>20=>3> A?V22V4=>H5==O. # ?0FVT=BV2, O:V ?@89<0NBL :C<0@8=>2V 0=B8:>03C;O=B8,  
?@>B@><1V=>289 G0A ?>B@V1=> 287=0G0B8 4> ?>G0B:C B5@0?VW A8<20AB0B8=><, 0 B0:>6  
4>A8BL G0AB> =0 ?>G0B:C ;V:C20==O, I>1 ?5@5A2V4G8B8AO, I> =5 2V41C20;>AO 6>4=>W  
7=0G=>W 7B@><1V=>20=>3> G0AC. /: BV;L:8 4>AO30TBLAO AB01V;L=89 @V25=L ?@>B@>  
<1V=>2>3> G0AC, 9>3> ?>40;LH89 :=B@>;L 20@B> ?@>2>48B8 7 V=B5@20;0<8, I> 70728G09 @5:>  
<5=4CNBLAO 4;O ?0FVT=BV2, O:V >45@6CNBL B5@0?VN :C<0@8=>28<8 0=B8:>03C;O=B0<8. @8 7  
7C20==O 01> ?@8?8=5==V ?@89>

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

\$0@<0:>48=0

18<20AB0B8= 3V?>;V?V45 >B@8Aspergillus terreus, T =50:B82=8< ;@:B>=>;V7C 7 CB2>@5==O<  
3V4@>:A8:8A;>B=>3> ?>EV4=>3>, O:5 1;>;CT 3-3V4@>:A8-3-<5B8;-3;CB0@8;->-@54C:B07C (->A  
@54C:B07C), D5@<5=B, I> :0B0;V7CT ?>G0B:>2C @50:FVN CB2>@5==O <520;>=0BC 7 ->. A:V;L:8  
?5@5B2>@5==O ->A 2 <520;>=0B O2;OT A>1>N @0==V9 5B0? A8=B57C E>;5AB5@8=C,



70AB>AC20==O A8<20AB0B8=C =5 A?@8G8=OT =0:>?8G5==O 2 >@30=V7B5=FV0;L=> B>:A8G=8E  
AB5@>;V2. ->A ;53:> <5B01>;V7CTBLAO 4> 0F5B8;->, I> 15@5 CG0ABL C 1030BL>E  
1V>A8=B5B8G=8E ?@>F5A0E 2 >@30=V7?@>B5W4V2 =87L:>W IV;L=>ABV ()), ;V?>?@>B5W4V2  
4C65 =87L:>W IV;L=>ABV ()) V 7030;L=>3> E>;5AB5@8=C C ?;07783>B=>W AV<59=>W V =5AV  
<59=>W D>@<8 3V?5@E>;5AB5@8=5;8 ?V428I5=89 2;5AB5@8=C T D0:B>@<< @878:C). @5?0@0B  
?V428ICT 2?@>B5W4V2 28A>:>W IV;L=>ABV ()), 7<5=HCT A?V22V4=>H5==O )/ V 7030;L=89  
E>;5AB5@8=/. !?>2V;L=NT ?@>3@5AC20==O :>@>=0@=>3> 0B5@>A.;5@>7C V 7=86CT O:  
G0AB>BC 28=8:=5==O =>28E C@065=L, B0: V 9<>2V@=VABL @>728B:C B>B0;L=8E >;N7V9 AC48=  
>G0B>: 4VW ?@5?0@0BC A?>AB5@V30TBLAO G5@57 2 B86=V ?VA;O ?>G0B:C 9>3> ?@89>  
;5AB5@8=C ?>25@B0TBLAO 4> ?>G0B:>2>3> @V2=O, I> A?>AB5@V302AO 4> ?>G0B:C ;V:C20==O.  
D5:B82=89 O: C 283;04V <=>B5@0?VW, B0: V C A?>;CG5==V 7V A5:25AB@0=B0-8 6>2G=8E :8A;>B.  
\$0@<0:>:V=5B8:0.

1A>@1FVO A8<20AB0B8=C 28A>:0. VA;O ?5@>@0;L=>3> ?@89>AO3=5==O <0:A8<0;L=>W  
:=F5=B@0FVW 4VNG>W @5G>28=8 C ?;072V AB0=>28BL 1,3-2,4 3>48=8 V 7=86CTBLAO =0 90 %  
G5@57 12 3>48= ?VA;O ?5@H>3> 9>3> ?@89>=F5=B@0FVO 0:B82=>W D>@<8 C A8AB5<=>2>B>FV  
AB0=>28BL <5=H5 5 % 2V4 ?5@>@0;L=> ?@89=OB>W 4>78. 2O7>: 7 1V;:0<8 ?;07<8 AB0=>28BL 95 %.  
18<20AB0B8= <5B01>;V7CTBLAO C ?5GV=FV, <0T 5D5:B <?5@H>3> ?@>E>465==O» G5@57 ?5GV=:C  
(2 >A=>2=>;V7CTBLAO C A2>N 0:B82=C D>@:A8:8A;>BC, 28O2;5=V 9 V=HV 0:B82=V, 0 B0:>6  
=50:B82=V <5B01>;VB8), 7 ?>40;LH>N 5:A:@5FVTN 2 6>2G. 5@V>4 =0?V2282545==O 7 >@30=V73>  
0:B82=8E <5B01>;VBV2 AB0=>28BL 1;87L:> 3 3>48=. >;2=8< G8=>< 60 % A8<20AB0B8=C  
282>48BLAO 7 :0;>28<8 <0A0<8 C 283;04V <5B01>;VBV2. ;87L:> 10-15 % A8<20AB0B8=C 282>48BLAO  
=8@:0<8 2 =50:B82=V9 D>@

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

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

"5@ABV. 1,5 @>:C.

#<>28 715@V30==O.

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

#?0:>2:0.

> 10 B01;5B>: C :=BC@=V9 G0@C=:>2V9 C?0:>2FV; ?> 2 :=BC@=V G0@C=:>2V C?0:>2:8 2 ?0GFV.

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

8@>1=8:.

@" «\$0@<0F52B8G=0 DV@<0 «0@=8FO».

VAF57=0E>465==O.

#: @0W=0, 02093, <. 8W2, 2C;. >@8A?V;LAL:0, 13.