

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

C□□\$□  
(SELOFEN)

!,:04:  
4VNG0 @5G>28=0: zaleplon;  
1 :0?AC;0 =C 10 <3;  
4>?>28=8: ;0:B>78 <=>3V4@0B, F5;N;>70 :@8AB0;VG=0, :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89,  
=0B@VN ;0C@8;AC;LD0B, =0B@VN :@>E<0;L3;V:>;OB (B8? ), <03=VN AB50@0B; A,:04 :0?AC;8:  
65;0B8=, B8B0=C 4V>:A84 (171), 70;V70 >:A84 G5@2>=89 (172), 70;V70 >:A84 G>@=89  
(172), 5@8B@>78= (127), V=483>:0@

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

\$0@<0:>B5@0?52B8G=0 3@C?0. !=>4V9=V B0 A540B82=V 70A>18. >4 "I N05C F03.

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

>:070==O.

"O6:0 D>@<0 ?>@CH5==O A=C, I> ?@>O2;OTBLAO CB@C4=5==O< 70A8=0==O.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> :>5=BV2 ?@5?0@0BC. 5@V>4 3>4C20==O 3@C44N. "O6:0 ?5GV=:>20  
=54>AB0B=VABL. "O6:0 48E0;L=0 =54>AB0B=VABL. "O6:5 ?>@CH5==O DC=:FV9 =8@>:. !8=4@>  
=VG=>3> 0?=>5. "O6:0 18 @>:V2).

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

!5;>D5= ?@87=0G5=89 4;O 70AB>AC20==O C 4>@>A;8E.

5:>5=4>20=0 4>1>20 4>70 AB0=>28BL 10<3. 5 <>6=0 ?@89<0B8 4@C3C 4>7C ?@5?0@0BC 2 BC A0  
0:A8<0;L=0 B@820;VABL ;V:C20==O AB0=>28BL 2 B86=V.

;O >AV1 7 ?5GV=:>2>N =54>AB0B=VABN ;53:>3> 01> ?>3> ABC?5=O, =8@:>2>N =54>AB0B=VABN,  
E@>=VG=>N 48E0;L=>N =54>AB0B=VABN @5:>5=4CTBLAO 70AB>AC20==O 4>1>2>W 4>78 5 <3.  
5 A;V4 ?@89<0B8 70;5?;>= ?V4 G0A W6V 01> ?VA;O =5W, B>F5 70B@8@1FVN ?@5?0@0BC. V4 G0A  
70AB>AC20==O 70;5?;>=C =5 A;V4 26820B8 0;>3>;L.

!5;>D5= A;V4 70AB>A>2C20B8 157?>A5@54=L> ?5@54 2;:040==O< C ;V6:>,  
0FVT=B8 ?>E8;>3> 2V:C

5:>5=4CTBLAO 70AB>AC20==O 4>1>2>W 4>78 ?@5?0@0BC 5 <3, 2@0E>2CNG8 28A>:C  
GCB;82VABL 4> A=>4V9=8E ?@5?0@0BV2. /:I> F5 4>7C20==O 70157?5G8B8 =5<>6;82>,  
70AB>A>2C20B8 70;5?;>= B0:8< ?0FVT=B0< =5 A;V4.

VB8 B0 <>;>4L  
@5?0@0B ?@>B8?>:070=89 4;O 70AB>AC20==O 4VBO

@8 ?>@CH5==OE DC=:FV9 ?5GV=:8

# 72'O7:C 7V 7<5=H5=8< ;;V@5=A>< ?0FVT=B8 7 ;53:>N 01> ?>N ?5GV=:>2>N =54>AB0B=VABN  
?>28==V 70AB>A>2C20B8 4>7C ?@5?0@0BC 5 <3. /:I> F5 4>7C20==O 70157?5G8B8 =5<>6;82>,  
70AB>A>2C20B8 70;5?;>= B0:8< ?0FVT=B0< =5 A;V4. 0FVT=B0< 7 BO6:8<8 ?>@CH5==O<8 DC=:FV9  
?5GV=:8 70AB>AC20==O ?@5?0@0BC ?@>B8?>:070=>.

@8 ?>@CH5==OE DC=:FV9 =8@>:

\$0@<0:>:V=5B8:0 ?@5?0@0BC =5 7

>1VG=V @50:FVW.

86G5 =02545=V ?>1VG=V 5D5:B8 B0 G0AB>B0 WE=L>W ?>O28, O:V 2V4A;V465=L 70;5?;>=C.

!8AB5<=V ?>@CH5==O

5 4C65 G0AB> (>1/1000, <1/100): 0=>@5:AVO, 0AB5=VO, 7=865==O B0:B8;L=>W GCB;82>ABV, ?>30=5 A0<>?>GCBBO, D>B>A5=A81V;V70FVO.

I>:C F5=B@0;L=>W =5@2>2>W A8AB5<8 (&!)

'0AB> (>1/100, <1/10): 0<=57VO, ?0@5AB57VW, A>=;82VABL, 0B0:AVO, 457>@VT=B0FVO.

5 4C65 G0AB> (>1/1000, <1/100): ?>@CH5==O :>=F5=B@0FVW, 0?0BVO, 45?5@A>=0;V70FVO, 45?@5AVO, 70?0<>@>G5==O, 30;NF8=0FVW, 703>AB@5==O A;CEC, =NE>2V 30;NF8=0FVW, 48?;>?VO, =57207=5 <>2;5==O, ?>@CH5==O ?>;O 7>@C, 45?@5AVO, ?A8EVG=V B0 ?0@04>:A0;L=V @50:FVW, 7=865==O :>=F5=B@0FVW, 3V?5AB57VO, 0<=57VO.

'0AB>B0 =5 287=0G5=0: A><=0<1C;V7

I>:C >@30=V2 7>@C

5 4C65 G0AB> (>1/1000, <1/100): ?>@CH5==O 7>@C, 42>W==O 2 >G0E.

I>:C >@30=V2 A;CEC

5 4C65 G0AB> (>1/1000, <1/100): 703>AB@5==O A;CEC.

I>:C H;C=:>2>-.8H:>2>3> B@0:BC

5 4C65 G0AB> (>1/1000, <1/100): =C4>B0.

'0AB>B0 =5 287=0G5=0: ?V428I5==O @V2=O B@0=A0

I>:C AB0B52>W A8AB5<8

'0AB> (>1/100, <1/10): 0;L3>48A<5=>@5O.

I>:C VW A8AB5<8

C65 @V4:> (<1/10 000): 0=0DV;0:B8G=V B0 ?A524>0=0DV;0:B8G=V @50:FVW.

'0AB>B0 =5 287=0G5=0: 0=3V>=52@>B8G=89 =01@O:.

>@CH5==O 7 I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=

5 4C65 G0AB> (>1/1000, <1/100): @50:FVW ?V428I5=>W GCB;82>ABV =0 A2VB;>.

'0AB>B0 =52V4><0: 0=3V>=52@>B8G=89 =01@O:.

>@CH5==O <5B0I>;V7

5 4C65 G0AB>: 0=>@5:AVO.

030;L=V ?>@CH5==O B0 AB0=8 C

5 4C65 G0AB>: 0AB5=VO, ?>30=5 A0<>?>GCBBO.

>@CH5==O 7 I>:C ?5GV=:8 B0 6>2G=8E H;OEV2

'0AB>B0 =52V4><0: 35?0B>B>:A8G=VABL (O: ?V428I5=0 0:B82=VABL @B@0=AD5@07).

A8EVG=V ?>@CH5==O

5 4C65 G0AB>: 45?5@A>=0;V70FVO, 30;NF8=0FVW, 45?@5AVO, @>73C1;5=VABL, 0?0BVO.

'0AB>B0 =52V4><0: A><=0<1C;V7

<=57VO

<=57VO <>65 =0ABC?0B8 =02VBL ?@8 70AB>AC20==V B5@0?52B8G=8E 4>7. 878: 28=8:=5==O 0

<=57VW 71V;LHCTBLAO ?@8 ?@89>7 ?@5?0@0BC. <=57VO <>65 1CB8 ?>2O70=0 7 =5B8?>2>N

?>254V=:>N.

5?@5AVO

V4 G0A 70AB>AC20==O ?@5?0@0BC !5;>D5= <>65 =0ABC?8B8 @5F8482 @0=VH5 VA=CNG>W

45?@5AVW.

A8EVG=V B0 ?0@04>:A0;L=V @50:FVW

V4 G0A 70AB>AC20==O 15=7>4V075?V=C B0 ?>EV4=8E <>6CBL 7O28B8AO B0:V ?>1VG=V O28I0, O::

70=5?>:>T==O, 71C465==O, 4@0BV2;82VABL, =5:>=B@>;L>20=V @50:FVW, 0=><0;L=5 <8A;5==O,

03@5A82=VABL, <0@5==O, =0?048 3=V2C, =VG=V :>H<0@8, 45?5@A>=0;V70FVO, 30;NF8=0FVW,

?A8E>78, =5B8?>20 ?>254V=:0, 5:AB@025@AVO, I> =5 2V4?>2V40T E0@0:B5@C ?0FVT=B0, 0 B0:>6

V=HV ?>@CH5==O ?>254V=:8. B0:>1VG=V O28I0 =09G0ABVH5 7O2;ONBLAO 2 4VB59 B0 >AV1

;VB=L>3> 2V:C.

0:56=VABL

0AB>AC20==O !5;>D5=C 2 B>70E <>65 ?@8725AB8 4> DV78G=>W 70;56=>ABV. V404:8 7;>26820==O

15=7>4V075?V=V2 B0 ?>4V1=8E ?@5?0@0BV2.

5@54>7C20==O.

0 40=89 G0A 7V1@0=> =54>AB0B=L> 40=8E AB>A>2=> ?5@54>7C20==O 70;5?;>=C. !8<8

?5@54>7C20==O ?>2O70=V 7 ?>A8;5==O< 4VW ?@5?0@0BC, I> ?@872>48BL 4> 7030;L1>B8 &!; 2V4

A>=;82>ABV 4> :><8.

!8<8 ;53:>3> ?5@54>7C20==O: A>=;82VABL, 457>@VT=B0FVO, ;5B0@3VO;  
@8 206:>7C20==V <6CBL =0ABC?0B8: 0B0:AVO, 7=865==O 7030;L=>3><07>2>3> B>=CAC,  
0@B5@V0;L=0 3V?>B5=7VO, ?@83=VG5==O 48E0==O, @V4:> :><0, 4C65 @V4:> A<5@BL.  
5@54>7C20==O 70;5?;>=C AB0=>28BL 703@>7C 4;O 68BBO >AV1, O:V ?@89<0NBL V=HV 70A>18, I>  
?@83=VGCNBL &! (C B>3>;L).  
# 28?04:C ?5@>@0;L=>3> ?5@54>7C20==O 15=7>4V075?V=V2 B0 ?@5?0@0BV2 V7 AE>6>N 4VTN  
A;V4 A?@>2>:C20B8 1;N20==O (?@>BO3<< >4=VTW 3>48=8), O:I> ?0FVT=B ?@8B<=<89, 01>  
?@>25AB8 ?@><820==O H;C=:0, 70157?5G82H8 ?@>EV4=VABL 48E0;L=8E H;OEV2, O:I> ?0FVT=B  
=5?@8B<=<89. /:I> ?@><820==O H;C=:0 =5 40T 5D5:BC, A;V4 70AB>AC20B8 0:B82>20=5 2C3V;;O 4;O  
1>B8 F5=B@0;L=>W =5@2>2>W A8AB5<8, 2V4 A>=;82>ABV 4> :<8.  
V:C20==O: ?>:070=> ?@>2545==O ?V4B@8W V A8<0B8G=>W B5@0?VW.  
/:I> ?0FVT=B ?@8B<=<89, A;V4 A?@>2>:C20B8 1;N20==O 01> ?@>25AB8 ?@><820==O H;C=:C B0  
225AB8 A>@15=B 4;O  
VA;O ?5@54>7C20==O 70;5?;>=C A?>AB5@V30;0AL E@><0BC@VO.

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

03VB=VABL

03VB=V 6V=:8 =5 ?>28==V ?@89<0B8 70;5?;>= C 7207:C V7 2V4ACB=VABN ;V=VG=8E 4>A;V465=L 70  
CG0ABN 203VB=8E.

V=:C D5@B8;L=>3> 2V:C A;V4 ?>?5@548B8 ?@> =5>1EV4=VABL ?@8?8=5==O ;V:C20==O !5;>D5=× 2  
@07V 70?;0=>20=>W 01> ?5@5410GC20=>W 203VB=>ABV.

/:I> 70 <548G=8<8 ?>:070==O<8 !5;>D5= ?@87=0G0TBLAO ?@>BO3<< >AB0==VE ABV 01> ?V4 G0A  
?>;>3V2, A;V4 >GV:C20B8 2?;82C 70;5?;>=C =0 =>2>=0@>465=>3>. # FL>B5=7VO, 01> ?> I> =5<>2;OB0  
6V=>., O:V ?V4 G0A 203VB=>ABV (C 4@C3V9 ?>;>28=V 203VB=>ABV) B@820;> ?@89<0;8 ?@5?0@0B,  
<0B8=C ?VA;O =0@>465==O.

0:B0FVO

0;5?;>= C =525;8:V9 :V;L:>ABV 284V;OTBLAO 7 3@C4=8< <>;>× (<0:A8<0;L=0 :>=F5=B@0FVO  
4>AO30TBLAO ?@>BO3<< 1 3>48=8 ?VA;O ?@89>A:V;L:8 =52V4<<89 2?;82 70;5?;>=C =0 48B8=C, 9>3>  
=5 A;V4 @5:><5=4C20B8 6V=:0<, O:V 3>4CNBL 3@C44N.

**VB8.**

0 40=89 G0A =54>AB0B=L> ;V=VG=8E 40=8E AB>A>2=> 70AB>AC20==O 70;5?;>=C C 4VB59, B>  
A>2C20B8 ?@5?0@0B 4VBO< ?@>B8?>:070=>.

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

V:C20==O ?>28==> 1CB8 =0ABV;L:8 :>@>B:8<, =0A:V;L:8 F5 <>6;82>, <0:A8<0;L=0 B@820;VABL<>65  
AB0=>28B8 2 B86=V.

0AB>AC20==O !5;>D5=C <>65 ?@8725AB8 4> ?A8EVG=>W B0 DV78G=>W 70;56=>ABV. 878:

@>728B:C 70;56=>ABV 71V;LHCTBLAO ?@>?>@FV9=> 4>7V B0 B@820;>ABV ;V:C20==O. "0:>6 2V=  
28I89 C ?0FVT=BV2, O:V 7;>26820NBL 0;>3>;5< V A=>4V9=8<8 ?@5?0@0B0<8.

!;V4 ?>2V4<<8B8 ?0FVT=B0 ?@> <>6;82VABL @5F8482C 157A>==O ?VA;O 70:V=G5==O ;V:C20==O.

!5;>D5= <>65 A?@8G8=OB8 ?@>3@5ACNGC 0<=57VN B0 ?A8E<<B>@>=V ?>@CH5==O G5@57 :V;L:0  
3>48= ?VA;O ?@89>1 7=878B8 @878: 28=8=:5==O F8E ?>1VG=8E O28I, ?0FVT=B =5 ?>28=5=  
28:>=C20B8 4VW, I> ?>B@51CNBL ?A8E<<B>@>=W :>>@48=0FVW, ?@8=09<=V ?@>BO3<< 4 3>48=  
?VA;O ?@89>

# ?0FVT=BV2, O:V 26820NBL A=>4V9=V B0 70A?>:V9;82V ?@5?0@0B8, ?VA;O WE 70AB>AC20==O

A?>AB5@V30;8AO ?>@CH5==O ?>254V=:8 C AB0=V =5?>2=>W A2V4<<ABV, V7 >1>@>B=>N 0

<=57VTN. &V O28I0 <>6CBL ?@>O2;OB8AO C ?0FVT=BV2, O:V @0=VH5 =5 ;V:C20;8AO 01>

;V:C20;8AO A=>4V9=8<8 B0 70A?>:V9;828<8 ?@5?0@0B0<8. "0:5 O28I5, O: :5@C20==O B@0=A?>@B=8

<8 70A>10<8 C =0?V2A=V, <>65 A?>AB5@V30B8AO ?V4 G0A 26820==O ;8H5 A=>4V9=8E B0

70A?>:V9;828E ?@5?0@0BV2 C B5@0?52B8G=8E 4>70E, 0;5 @878: 28=8=:5==O B0:>3> AB0=C

71V;LHCTBLAO ?@8 26820==V 0;>3>;N B0 V=H8E @5G>28=, O:V <0NBL 30;L2C A8AB57, O:V

?5@528ICNBL <0:A8<0;L=C @5:><5=4>20=C 4>7C. # 7207:C V7 703@>7>N 4;O ?0FVT=B0 B0 4;O

>B>GCNG8E @5:><5=4CTBLAO 2V4<>28B8AO 2V4 26820==O 70;5?;>=C ?0FVT=B0<, C O:8E @0=VH5

265 A?>AB5@V30;>AO B0:5 O28I5, O: :5@C20==O B@0=A?>@B=8<8 70A>10<8 C =0?V2A=V. VA;O  
268BBO A=>4V9=8E B0 70A?>:V9;828E ?@5?0@0BV2 A?>AB5@V30;8AL B0:>6 V=HV ?>@CH5==O  
?>254V=:8 (=0?@8::04, 3>BC20==O B0 26820==O W6V, B5;5D>==V @>7<>28, AB0B52V 0:B8 C AB0=V  
=5?>2=>W A2V4<>ABV). 0FVT=B8 70728G09 =5 ?0<OB0NBL F8E ?>4V9.  
V4 G0A 26820==O A=>4V9=8E B0 70A?>:V9;828E ?@5?0@0BV2, C B>C, A?>AB5@V30;8AO B06:V  
0=0DV;0:B8G=V B0 0=0DV;0:B>W4=V @50:FVW. VA;O 70AB>AC20==O ?5@H>W 4>78 01> G5@3>28E  
4>7 A?>AB5@V30;8AO 28?04:8 0=3V>=52@>B8G=>3> =01@O:C, I> >E>;N202 O78:, 3>;>A>2C IV;8=C  
B0 3>@B0=L. # 45O:8E ?0FVT=BV2, O:V ?@89<0;8 A=>4V9=V B0 70A?>:V9;82V ?@5?0@0B8,  
7O2;O;8AO 4>40B:>2V A8<8, B0:V O: 7048H:0, 2V4GCBBO 70B8A:0==O 3>@;0 01> =C4>B0 V  
1;N20==O. 5O:8< ?0FVT=B0< 1C;0 =5>1EV4=0 3>A?VB0;V70FVO B0 B5@25 ;V:C20==O. /:I>  
0=3V>=52@>B8G=89 =01@O: >E>;NT O78:, 3>;>A>2C IV;8=C B0 3>@B0=L, <65 =0ABC?8B8  
=5?@>EV4=VABL 25@E=VE 48E0;L=8E H;OEV2, O:0 ?@872>48BL 4> A<5@BV. 5 A;V4 ?>2B>@=>  
70AB>A>2C20B8 70;5?;>= ?0FVT=B0<, C O:8E ?VA;O 9>3> 70AB>AC20==O 28=8:02  
0=3V>=52@>B8G=89 =01@O:..  
57A>==O <>65 A?@8G8=OB8AO DV78G=8<8 B0 ?A8EVG=8<8 ?>@CH5==O<8. 57A>==O, O:5 =5  
?@>E>48BL 01> ?>A8;NTBLAO ?VA;O :>@>B:>G0A=>3> 70AB>A>2C20==O 70;5?;>=C, <>65  
A2V4G8B8 ?@> ?>B@51C ?>2B>@=>3> >1AB565==O ?0FVT=B0.  
5@V>4 =0?V2282545==O 70;5?;>=C :>@>B:89 V B@820T 1 3>48=C. /:I> ?0FVT=B ?@>:840TBLAO @0=>  
2@0=FV, A;V4 28@VH8B8 ?8B0==O ?@> 70AB>AC20==O 0;LB5@=0B82=>W B5@0?VW. 0FVT=B0  
A;V4 ?>?5@548B8 ?@> =5<>6;82VABL ?@89>W 4>78 !5;>D5=C 2 BC A0  
0AB>AC20==O 70;5?;>=C @07>< 7 V=H8<8 ?@5?0@0B0<8, I> 2?;820NBL =0 CYP3A4, <>65 7  
=F5=B@0FVN 70;5?;>=C.  
@5?0@0B =5?@840B=89 4;O ;V:C20==O 45?@5AVW V AB0=C ?V428I5=>W B@82>6=>ABV.  
@5?0@0B 78, 7=865=8< @V2=5< ;0:B078 B8?C Lapp 01> ?>@CH5==O<8 2A<>:BC20==O ;0:B>78-  
30;0:B>78 =5 ?>28==V ?@89<0B8 ?@5?0@0B !5;>D5=.  
0AB>AC20==O ?@5?0@0BC !5;>D5= >A>10< ?>E8;>3> 2V:C  
0;5?;>= <>6=0 70AB>A>2C20B8 >A>10< ?>E8;>3> 2V:C. \$0@<0>:V=5B8:0 70;5?;>=C 4;O =8E >A>1;82>  
=5 2V4@V7=OTBLAO 2V4 D0@<0>:V=5B8:8 70;5?;>=C C <>;>4H8E ;N459. 5:<>5=4CTBLAO  
4>7C20==O 5 <3 7 >3;O4C =0 1V;LHC GCB;82VABL =0 4VN A=>4V9=8E 70A>1V2.  
0AB>AC20==O ?@5?0@0BC !5;>D5= ?0FVT=B0< V7 ?>@CH5==O<8 DC=:FVW ?5GV=:8  
0FVT=B0< 7 206:>N ?5GV=:>2>N =54>AB0B=VABN =5 A;V4 ?@87=0G0B8 70;5?;>=. 0FVT=B0< 7 ;53:8  
<8 B0 ?>9 ?5GV=:8 =5>1EV4=0 :>@5:FVO 4>78 ?@5?0@0BC 7 ?@82>4C 71V;LH5=>W  
1V>4>ABC?=>ABV 70;5?;>=C.  
0AB>AC20==O ?@5?0@0BC !5;>D5= ?0FVT=B0< V7 ?>@CH5==O<8 DC=:FVW =8@>:  
>AV1 7 =8@>2>N =54>AB0B=VABN D0@<0>:V=5B8:0 70;5?;>=C >A>1;82> =5 2V4@V7=OTBLAO 2V4  
D0@<0>:V=5B8:8 C 74>@>28E ;N459, >4=0: 2 =8E 1V;LH0 9<>2V@=VABL 71V;LH5=>W  
:>=F5=B@0FVW =50:B82=8E <5B01>;VBV2 70;5?;>=C.  
8E0;L=0 =54>AB0B=VABL  
!;V4 4>B@8A>1;82>W >15@56=>ABV ?@8 ?@87=0G5==V !5;>D5=C ?0FVT=B0< 7 E@>=VG=>N  
48E0;L=>N =54>AB0B=VABN.

#### A8E>78

5 A;V4 70AB>A>2C20B8 ?@5?0@0B B0 ?>EV4=V 15=7>4V075?V=C 4;O 107>2>3> ;V:C20==O ?A8E>7C.  
0AB>AC20==O >A>10<, I> 7;>26820NBL 0:>3>;5< 01> ;V:C20;L=8<8 ?@5?0@0B0<8  
!;V4 1CB8 4C65 >15@56=8<8, 70AB>A>2CNG8 15=7>4V075?V= B0 ?@5?0@0B8 AE>6>W 4VW C FV9  
3@C?V ?0FVT=BV2.

#### 5?@5AVO

5=7>4V075?V=8 B0 ?@5?0@0B8 7V AE>6>N 4VTN =5 A;V4 70AB>A>2C20B8 2<>=>B5@0?VW  
45?@5AVW 01> B@82>6=>ABV, ?>2'O70=>W 7 45?@5AVTN. # 72'O7:C V7 1V;LH8 @878:<< A2V4>  
<>3> ?5@54>7C20==O 2 >AV1 7 45?@5AVTN :V;L:VABL @5:×5=4>20=>3> F8< ?0FVT=B0<  
?@5?0@0BC, 2 B>=C, A;V4 >1<568B8 4> =5>1EV4=>3>

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>I>BV 7  
V=H8<8 <5E0=V7<0<8.

@5?0@0B 7=0G=> 2?;820T =0 740B=VABL :5@C20B8 B@0=A?>@B=8<8 70A>10<8 B0 >1A;C3>2C20B8  
<5E0=VG=V ?@8AB@>W. !=;82VABL, 0=57VO, ?>@CH5==O :=F5=B@0FVW, ?>@CH5==O  
DC=:FV>=C20==O <07V2 ?>3V@HCNBL 740B=VABL :5@C20B8 B@0=A?>@B=8<8 70A>10<8 B0  
>1A;C3>2C20B8 <5E0=VG=V ?@8AB@>W. # @07V =54>AB0B=L>W B@820;>ABV A=C  
71V;LHCTBLAO 9<>2V@=VABL ?>@CH5==O C2038.  
0FVT=B0<, 4VO;L=VABL O:8E ?>B@51CT 7=0G=>W ?A8E>DV78G=>W 0:B82=>ABV, B0:>6 A;V4 1CB8  
>15@56=8<8.

!5;>D5= 2?;820T =0 H284:VABL ?A8E<>B>@=8E @50:FV9, B>3> =5 <>6=0 ?@87=0G0B8 ?0FVT=B0<,  
4VO;L=VABL O:8E ?>B@51CT ?V428I5=>W C2038 B0 7=0G=>W ?A8E<>B>@=>W 0:B82=>ABV.

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

;:>3>;L=5 @5:><5=4CTBLAO >4=>G0A=5 70AB>AC20==O V7 70;5?;>=>< C 7207:C V7 ?>A8;5==O<  
9>3> A540B82=>W 4VW. &5 >1<56CT ?A8EVG=V B0 DV78G=V @50:FVW B0 7=86CT 740B=VABL 4>  
:5@C20==O B0 >1A;C3>2C20==O <5E0=VG=8E ?@8AB@>W2.  
!;V4 4>B@815@56=>ABV C @07V >4=>G0A=>3> 70AB>AC20==O V7 70A>10<8, I> 2?;820NBL =0  
F5=B@0;L=C =5@2>2C A8AB5:V9;820 4VO <>65 ?>A8;N20B8AL C @07V ?>T4=0==O 7 B0:8<8 70A>10  
<8: ?@5?0@0B8, I> 70AB>A>2CNBLAO ?@8 ?A8EVG=8E 70E2>@N20==OE (0=B8?A8E>B8G=V,  
A=>4V9=V, 0=:AV>;VB8G=V, A540B82=V, 0=B845?@5A82=V 70A>18), ?@5?0@0B8, I>  
70AB>A>2CNBLAO ?@8 ;V:C20==V A8;L=>3> 1>;N (>?V>W4=V 0=0;L35B8:8), ?@5?0@0B8 4;O  
;V:C20==O =0?04V2 AC4< (0=B85?V;5?B8G=V ?@5?0@0B8), 0=5AB57C20;L=V ?@5?0@0B8,  
?@5?0@0B8, I> 70AB>A>2CNBLAO C ;V:C20==V 0;5@3VW (0=B83VAB0N 4VTN).  
5=;0D0:A8= (C 4>7V 75 <3 01> 150 <3 =0 4>1C, C ;V:0@AL:V9 D>@4>265=8< 282V;L=5==O<), I>  
70AB>A>2CTBLAO 2 :><1V=0FVW 7 10 <3 70;5?;>=C, =5 7C<>2;NT ?>@CH5=L ?0<OBV  
(157?>A5@54=T B0 2V4AB@>G5=5 7304C20==O A;V2) 01> ?A8E<>B>@=8E @50:FV9 (B5AB  
?V4AB0=>2:8 F8D@>28E A8<2>;V2). @V< B>3>, =5 2V4=>< B0 25=;0D0:A8=>< (C ;V:0@AL:V9 D>@  
4>265=>N 4VTN).

# @07V 70AB>AC20==O 7 >?V>W4=8<8 0=0;L35B8:0<8 <>65 ?>A8;8B8AO 59D>@V9=0 4VO, O:0  
?@872>48BL 4> 71V;LH5==O DV78G=>W 70;56=>ABV.

&8<5B848= (=5A?5F8DVG=89, ?> ?>BC6=89 V=3V1VB>@ ?5GV=:>28E D5@<5=BV2, =0?@8:;04  
>:A84078 B0 !YP3A4) ?V428ICT :=F5=B@0FVN 70;5?;>=C 2 ?;072C >:A8407C B0 !YP3A4 (5=78<8, I> 7C  
<>2;NNBL <5B01>;V7< 70;5?;>=C). ">15@56=> 70AB>A>2C20B8 FV ?@5?0@0B8 >4=>G0A=>.  
0AB>AC20==O ?@5?0@0BC !5;>D5= >4=>G0A=> 7 800 <3 5@8B@> <>65 2V41CB8AO  
?>B5=FVN20==O 9>3> A540B82=>W 4VW.

8D0 O: A8;L=89 V=4C:B>@ D5@<5=BV2 ?5GV=:8, =0?@8:;04 !YP3A4, <>65 A?@8G8=8B8 7<5=H5==O  
:=F5=B@0FVW 70;5?;>=C C G>B8@8 @078. @5?0@0B8-V=48:0B>@8 !YP3A4, B0:V O: @8D0  
10@1VB0; , ?@8 >4=>G0A=>AC20==V 7 ?@5?0@0B< !5;>D5= <>6CBL 7<5=H8B8 5D5:B82=VABL  
70;5?;>=C.

0;5?B>=5 2?;820T =0 D0@<0>:V=5B8:C V D0@<0>48=0:A8=C V 20@D0@8=C 7 2C7L:8< ;V:C20;L=8<  
V=45:A>

IC?@>D5=, I> 2?;820T =0 =8@:>25 284V;5==O, ?@8 >4=>G0A=>AC20==V V7 70;5?;>=>< =5  
A?@8G8=OT 4>40B:>2>W 270T<>4VW.

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

\$0@<0>48=0 0;5?;>= T ;V:0@AL:8< 70A>1>< 7 3@C?8 ?V@07>;?V@84V075?V=V2 B0 V=H8E  
A=>4V9=8E 70A>1V2. 0;5?;>= 270T<>4VT 7 15=7>4V075?V=>28< @5F5?B>@>< A, I> ==8E  
AB@C:BC@0E F5=B@0;L=>W =5@2>2>W A8AB5<8 (&!).

\$0@<0>:V=5B8G=89 ?@>DV;L 70;5?;>=C 45<=>AB@CT H284:5 ?>3;8=0==O B0 282545==O. 81V@:>2>  
72'O7CTBLAO 7 15=7>4V075?V=>28<8 @5F5?B>@0<8 I B8?C.

\$0@<0>:V=5B8G=V 2;0AB82>ABV.

1A>@1FVO

0;5?;>= ?VA;O ?5@>@0;L=>3> 70AB>AC20==O H284:> V ?@0:B8G=> ?>2=VABN 2A<:BCTBLAO C  
H;C=:>2>-8H:>2>(C<sub>max</sub>) C A8@>20BFV 4>AO30TBLAO ?@>BO3< ?@81;87=> 1 3>48=8. 0;5?;>=  
1V>B@0=AD>@3> 1V>4>ABC?=VABL AB0=>28BL 1;87L:> 30%.

>7?>4V;

0;5?;>= ;V?>DV;L=89, 0 >1T< 9>3> @>7?>4V;C ?VA;O 2=CB@VH=L>25==>3> 70AB>AC20==O A;;040T  
1;87L:> 1,4 □ 0,3 ;/:3. C<>20E *in vitro* 2V= ?@81;87=> =0 60% 72O7CTBLAO 7 1V;;0<8 ?;07<8, I> 2:07CT =0  
=525;8:89 @878: ?>O28 270T<>4VW 4VNG>W @5G>28=8 2=0A;V4>: 72O7C20==O 7 1V;;0<8.

V>B@0=AD>@<0FVO

0;5?;>= 1V>B@0=AD>@A=>2=>:A8-70;5?;>= ?V4 4VTN D5@<5=BC 0;L453V4>:A84078. 5=H>N N  
B@0=AD>@D5@<5=B>< 34 F8B>E@>450 4> 485B8;70;5?;>=C V ?>BV< 4> 5->:A8-485B8;70;5?;>=C. 0;V  
>18420 <5B01>;VB8, 5->:A8-70;5?;>= V 5->:A8-485B8;70;5?;>=, B@0=AD>@ 3;N:C@>=V4V2 V  
282>4OBLAO 7 A5G5N. >A;V465==O *in vitro* =0 B20@8=0E ?>:070;8, I> <5B01>;VB8 70;5?;>=C D0@  
<0>;>3VG=> =50:B82=V. >=F5=B@0FVO 70;5?;>=C C ?;07, =5 28O2;5=> :C=C ?VA;O 70AB>AC20==O 4>  
30 <3/4>1C. 5@V>4 =0?V2282545==O 70;5?;>=C A;;040T ?@81;87=> 1 3>4.

82545==O

0;5?;>= 282>48BLAO C D>@< (17%). V;LHVABL (57%) 70AB>A>20=>W 4>78 282>48BLAO 7 A5G5N C  
D>@:A8-70;5?;>=C V 9>3> ?>EV4=8E 3;N:C@>=V4V2, I5 9% 282>4OBLAO C D>@:A8-485B8;70;5?;>=C  
V 9>3> ?>EV4=8E 3;N:C@>=V4V2. =H0 G0AB8=0 4>78 F5 <5=H 206;82V <5B01>;VB8, I> 282>4OBLAO  
7 A5G5N. V;LHVABL<5B01>;VBV2, O:V 1C;8 28O2;5=V C :0;V, - F5 5->:A8-70;5?;>=.

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

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 7 @>6528< :>@?CA>< B0 1;0:8B=>N  
:@8H5G:>N @>7 @>H>:.

"5@ABV. 4 @>:8.

#<>28 715@V30==O. 15@V30B8 ?@8 B5 +25□, C ACE>ABC?=>

#?0:>2:0. > 10 :0?AC; C 1;VAB5@V; ?> 1 01> 2 1;VAB5@8 C :0@B>==V9 ?0GFV.

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

8@>1=8:8 B0 465==O.

1. ", >;LI0.
2. 01 O=VFL:89 D0@<0F52B8G=89 702>4 >;LD0 .", >;LI0.

1. 5=L:>2 149, 05-152 'A=>2, >;LI0.
2. C;. 0@H. 6. V;AC4AL:>3> 5, 95-200 01'O=VF5, >;LI0.