

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

®
(ZODAC®)

!::04:

4VNG0 @5G>28=0: F5B8@878=C 483V4@>E;>@84;
5 <; A8@>?C E;>@84C 5 <3;
4>?>28=8: <5B8;?0@015= (218), ?@>?V;?0@015= (216), 3;VF5@8= (85 %), ?@>?V;5=3;V:>;L, A>@1VBC
@>7G8=, I> =5 :@8AB0;V7CTBLAO (420), A0E0@8= =0B@VN, =0B@VN 0F5B0BC B@83V4@0B,
:8A;>B0 >FB>20 ;L>4O=0, 0@><0B870B>@ 10=0=>289 75420-33, 2>40 >G8I5=0.

V:0@AL:0 D>@<0. !8@>?.

A=>2=V DV78:>-EVABV: ?@>7>@89, 2V4 15710@2=>3> 4> ;54L 6>2BC20B>3> :>;L>@C A8@>?.

\$0@<0:>B5@0?52B8G=0 3@C?0. □=B83VAB018 4;O A8AB5<=>3> 70AB>AC20==O. >EV4=V
?V?5@078=C. >4 "% R06A □07.

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

\$0@<0:>48=0

?VB 3V4@>:A878=C C ;N48=8, T ?>BC6=8< V A5;5:B82=8< 0=B03>=VAB< ?5@8D5@8G=8E H1-
@5F5?B>@V2. # E>4V 4>A;V465=L in vitro 7 282G5==O 7207C20==O 7 @5F5?B>@0<8 =5 1C;> 28O2;5=>
0DV==>ABV, O:0 ?V440TBLAO 28 V=H8E @5F5?B>@V2, =V6 H1-@5F5?B>@8.

C;> ?>:070=>, I> >:@V< 0=B03>=VAB8G=>3> 5D5:BC =0 H1-@5F5?B>@8, F5B8@878= 45<>=AB@CT
?@>B80;5@3VG=C 4VN: 2 4>7V 10 <3 1 01> 2 @078 =0 4>1C 2V= V=3V1CT 78=>DV;V2 =0 ?V7=V9
AB04VW 0;5@3VG=>W @50:FVW =0 H:V@V B0 :=>N=:B82V >:0 C A5=A81V;V7>20=8E 0;5@35=<X
AC1T:BV2 7 0B>?VG=8<8 70E2>@N20==O<8.

E>4V 4>A;V465=L C 74>@>28E 4>1@>2>;LFV2 1C;> ?>:070=>, I> F5B8@878= C 4>70E 5 B0 10 <3
>?BC6=> V=3V1CT H:V@=V @50:FVW 70 B8?< «F2VBV==O», A?@8G8=5=V 4C65 28A>:8<8
:=>F5=B@0FVO<8 3VAB04=0: :=@5;OFVO 7 5D5:B82=VABN =5 1C;0 2AB0=>2;5=0.

E>4V 4>A;V465==O B@820;VABN 35 4=V2 C 4VB59 2V:< 2V4 5 4> 12 @>:V2 =5 A?>AB5@V30;>AO
728:0==O 4> 0=B83VAB0B> 5D5:BC (?@83=VG5==O @50:FVW 70 B8?< «F2VBV==O») F5B8@878=C.
VA;O ?@8?8=5==O B5@0?VW F5B8@878=< ?VA;O 1030B>:@0B=>3> 70AB>AC20==O =>@<0;L=0
@50:B82=VABL H:V@8 =0 3VAB0;N20;0AO 2?@>4>26 3 4=V2.

E>4V ?;0F51>:-:=B@>;L>20=>3> 4>A;V465==O B@820;VABN 6 B86=V2 7 CG0ABN 186 ?0FVT=BV2 7
0;5@3VG=8< @8=VB<< =0 B;V ;53:>W 01> A5@54=L>206:>W 1@>=EV0;L=>W 0AB<8 1C;> ?>:070=>, I>
F5B8@878= C 4>7V 10 <3 1 @07 =0 4>1C 7<5=HC202 A8<8 @8=VBC V =5 A?@8G8=02 74V FL>3>
4>A;V465==O 1C;0 ?V4B25@465=0 157?5G=VABL 70AB>AC20==O F5B8@878=C C ?0FVT=BV2 7
0;5@3VTN B0 ;53:>N G8 A5@54=L>206:>N 1@>=EV0;L=>N 0AB<N.

E>4V ?;0F51>:-:=B@>;L>20=>3> 4>A;V465==O 1C;> ?>:070=>, I> F5B8@878=, O:89 70AB>A>2C20;8 C
28A>:V9 4>1>2V9 4>7V 60 <3 2?@>4>26 7 4=V2, =5 A?@8G8=82 AB0B8AB8G=> 7=0GCI>3> ?>4>265==O
V=B5@20;C QT.

C;> ?>:070=>, I> ?@8 70AB>AC20==V 2 @5:><5=4>20=8E 4>70E F5B8@878= ?>:@0ICT O:VABL 68BBO
?0FVT=BV2 7 FV;>@VG=8< B0 A57>==8< 0;5@3VG=8< @8=VB>

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

0:A8<0;L=0 :=>F5=B@0FVO F5B8@878=C 2 ?;072V 2 @V2=>206=>28BL 1;87L:> 300 =3<; V
4>AO30TBLAO ?@>BO3>< 1,0 ± 0,5 3>48=8. VA;O 70AB>AC20==O F5B8@878=C 2 4>70E 10<3 I>45==>
2?@>4>26 10 4=V2 :C1C =5 A?>AB5@V30;>AO. >?>4V; D0@<0:>:V=5B8G=8E ?0@0<5B@V2, B0:8E O:
<0:A8<0;L=0 :=>F5=B@0FVO C ?;072V (Cmax) B0 ?;>I0 ?V4 D0@<0:>:V=5B8G=>N :@82>N (AUC), C
4>1@>2>;LFV2 (C ;N48=8) 1C2 >4=>@V4=8

!BC?V=L 01A>@1FVW F5B8@878=C =5 7<5=HCTBLAO ?@8 9>3> 70AB>AC20==V @07<< V7 W65N,
?@>B5 H284:VABL 01A>@1FVW ?@8 FL>4>ABC?=>ABV ?@8 70AB>AC20==V F5B8@878=C C D>@
<0E @>7G8=C, :0?AC; 01> B01;5B>: T 0=0;>3VG=8<8.

#O2=89 >1T< @>7?>4V;C AB0=>28BL 0,50;/:3. 2O7C20==O F5B8@878=C 7 1V;:0<8 ?;07<8 :@>2V
AB0=>28BL 93 ± 0,3%. &5B8@878= =5 7DV;L 72O7C20==O 20@D0@8=C 7 1V;:0<8 ?;07<8 :@>2V.
&5B8@878= ;8H5 =57=0G=>N N <5B01>;V7CTBLAO ?@8 ?5@H>E>465==V G5@57 ?5GV=:C. ;87L:>
42>E B@5B8= 4>78 5:A:@5BCTBLAO V7 A5G5N C =57 "5@4 =0?V2282545==O AB0=>28BL ?@81;87=>
10 3>48=.

&5B8@878= 45<>=AB@CT ;V=V9=C :V=5B8:C ?@8 70AB>AC20==V 4>7 C 4V0?07=>V 2V4 5 4> 60 <3.
A>1;82V 3@C?8 ?0FVT=BV2.

A>18 ;VB=L>3> 2V:C. VA;O ?5@>@0;L=>3> 70AB>AC20==O >4=>:@0B=>W 4>78 F5B8@878=C 10 <3 C
16 >AV1 ;VB=L>3> 2V:C ?5@V>4 =0?V2282545==O C =8E 71V;LHC202AO ?@81;87=> =0 50 %, 0
;V@5=A 7<5=HC202AO =0 40 % ?>@V2=O=> 7 >A>10<8 <>;>4H>3> 2V:C. <5=H5==O ;V@5=AC
F5B8@878=C C F8E 4>1@>2>;LFV2 ;VB=L>3> 2V:C 1C;> 0A>FV9>20=5 7V 7=865=>N DC=:FVTN
=8@>: C FV9 ?>?C;OFVW.

VB8, 2 B> 5@V>4 =0?V2282545==O F5B8@878=C AB0=>282 1;87L:> 6 3>48= C 4VB59 2V:< 6-12 @>:V2
V 5 3>48= C 4VB59 2V:< 2-6 @>:V2. # =5<>2;OB B0 <0;5=L:8E 4VB59 2V:< 2V4 6 4> 24 3,1 3>48=8.

0FVT=B8 7 ?>@CH5==O <8 DC=:FV9 =8@>:. \$0@<0>:V=5B8:0 ;V:0@AL:>3> 70A>1C C ?0FVT=BV2 7
;53:>N =8@>:2>N =54>AB0B=VABN (:;V@5=A :@50B8=V=C 1V;LH5 =V6 40<;/E2) B0 C 74>@>28E
4>1@>2>;LFV2 1C;0 0=0;>3VG=>N. # ?0FVT=BV2 V7 ?>N =8@>:2>N =54>AB0B=VABN ?5@V>4
=0?V2282545==O 71V;LHC202AO C 3 @078, 0 ;V@5=A 7<5=HC202AO =0 70 % ?>@V2=O=> 7 F8<8
?>:07=8:0<8 C 74>@>28E 4>1@>2>;LFV2.

?0FVT=BV2 =0 35<>4V0;V7V (:;V@5=A :@50B8=V=C <5=H5 =V6 7 <;/E2) ?VA;O ?5@>@0;L=>3>
70AB>AC20==O >4=>:@0B=>W 4>78 F5B8@878=C 10 <3 ?5@V>4 =0?V2282545==O 71V;LHC202AO C
3 @078, 0 ;V@5=A 7<5=HC202AO =0 70 % ?>@V2=O=> 7 F8<8 ?>:07=8:0<8 C >AV1 7 =>@<0;L=>N
DC=:FVTN =8@>:. &5B8@878= ;8H5 =57=0G=>N N 282>482AO ?@8 35<>4V0;V7V.# ?0FVT=BV2 7 ?>N
01> BO6:>N =8@>:2>N =54>AB0B=VABN =5>1EV4=> :>@83C20B8 4>7C (482. @>74V; «!?!>AV1
70AB>AC20==O B0 4>78»).

0FVT=B8 7 ?>@CH5==O <8 DC=:FV9 ?5GV=:8. # ?0FVT=BV2 V7 E@>=VG=8<8 70E2>@N20==O <8
?5GV=:8 (35?0B>F5;N;O@=89, E>;5AB0B8G=89 B0 1V;V0@=89 F8@>7 ?5GV=:8) ?VA;O
70AB>AC20==O >4=>:@0B=>W 4>78 F5B8@878=C 10 <3 01> 20 <3 ?5@V>4 =0?V2282545==O
71V;LHC202AO =0 50 %, 0 ;V@5=A 7<5=HC202AO =0 40 % ?>@V2=O=> 7 F8<8 ?>:07=8:0<8 C
74>@>28E >AV1.

?0FVT=BV2 7 ?>@CH5==O <8 DC=:FV9 ?5GV=:8 :>@83C20==O 4>78 ?>B@V1=> ;8H5 ?@8
>4=>G0A=V9 =0O2=>ABV C =8E ?>@CH5==O DC=:FVW =8@>:.

**;V=VG=V E0@0:B5@8AB8:8.
>:070==O.**

!8<0B8G=0 B5@0?VO =070;L=8E B0 >G=8E A8==>3> B0 ?>ABV9=>3> 0;5@3VG=>3> @8=VBC,
E@>=VG=>W V4V>?0B8G=>W :@>?82O=:8.

@>B8?>:070==O.

V?5@GCB;82VABL 4> 4VNG>W @5G>28=8, 3V4@>:A878=C, 1C4L-O:8E ?>EV4=8E ?V?5@078=C 01>
4> 1C4L-O:>W 7 4>?>28=.

0FVT=B8 7 BO6:>N =8@>:2>N =54>AB0B=VABN, 7 ;V@5=A< :@50B8=V=C <5=H5 =V6 10 <;/E2.
5 A;V4 70AB>A>2C20B8 F59 ;V:0@AL:89 70AV1 C ?0FVT=BV2 V7 @V4:VA=88 A?04:>28<8
70E2>@N20==O <8, ?>2'O70=8<8 7 =5?5@5=>A878.

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

@0E>2CNG8 ?@>DV;V D0@<0>:V=5B8:8, D0@<0>:48=0A8<>ABV F5B8@878=C, =VO:8E 270T<>4V9
?@8 70AB>AC20==V FL>3> 0=B83VAB0B> 70A>1C >GV:C20B8 =5 A;V4. 0 40=89 G0A C E>4V
4>A;V465=L 7 282G5==O ;V:0@AL:>W 270T<>4VW =5 ?>2V4<>;O;>AO =V ?@> D0@<0>:48=0
7=0GCIV D0@<0>:V=5B8G=V 270T<>4VW, C B>5D54@8=<< 01> B5>DV;V=<< (400 <3/4>1C).

4>A;V465==V 1030B>@07>2>3> 70AB>AC20==O @8B=>02V@C (600 <3 2 @078 =0 4>1C) B0
F5B8@878=C (10 <3 =0 4>1C) B@820;VABL 5:A?>78FVW 4> F5B8@878=C 71V;LH8;0AO ?@81;87=> =0
40 %, C B>9 G0A O: 48A?>78FVO @8B=>0 2V@C 45I> ?>@CHC20;0AO (-11 %) ?@8 >4=>G0A=>
5<0T 40=8E I>4> ?>A8;5==O 5D5:BC A540B82=8E 70A>1V2 ?V4 G0A 70AB>AC20==O ?@5?0@0BC.
1□T< 01A>@1FVW F5B8@878=C =5 7<5=HCTBLAO ?@8 9>3> 70AB>AC20==V @07<< V7 W65N,
?@>B5 H284:VABL 01A>@1FVW ?@8 FL>

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

C;> ?>:070=>, I> ?@8 70AB>AC20==V B5@0?52B8G=8E 4>7 40=>3> ?@5?0@0BC >4=>G0A=> 7 0;>3>;5
< (?@8 @V2=V 0;>3>;N C :@>2V 0,5 3/;) ;V=VG=> 7=0GCIV 270T<>4VW =5 A?>AB5@V30NBLAO.
@>B5 @5:><5=4>20=> C=8:0B8 >4=>G0A=>3> 26820==O 0;>3>;N.
5:><5=4CTBLAO 7 >15@56=VABN 70AB>A>2C20B8 F59 ?@5?0@0B C ?0FVT=BV2 7 5?V;5?AVTN B0 C
?0FVT=BV2 V7 @878:>< 28=8:=5==O AC4>
>15@56=VABN 70AB>A>2C20B8 ?0FVT=B0<, AE8;L=8< 4> 70B@8H:>465==O E@51B0, 3V?5@?;07VO
?@>AB0B8), B> F5B8@878= <>65 ?V428I8B8 @878: @>728B:C 70B@8
=B83VAB0IC, B>2545==O< 70AB>AC20==O ?@5?0@0BC =5>1EV4=> ?@8?8=8B8 70 3 4=V 4>
4>A;V465==O (?5@V>4 282545==O).
>15@56=VABN 70AB>A>2C20B8 ?@5?0@0B ?0FVT=B0< V7 E@>=VG=>N =8@:>2>N
=54>AB0B=VABLN (?>B@V1=0 :>@5:FVO @5687C20==O) B0 ?0FVT=B0< ;VB=L>3> 2V:C 7 =8@:>2>N
=54>AB0B=VABN (<>6;825 7=865==O ;C1>G:>2>W DV;LB@0FVW).
0AB>A>2C20B8 F59 ?@5?0@0B C =5<>2;OB B0 C <0;5=L:8E 4VB59 2V:>< <5=H5 =V6 2 @>:8 =5 @5:>
<5=4CTBLAO.
5 A;V4 70AB>A>2C20B8 F59 ;V:0@AL:89 70AV1 C ?0FVT=BV2 V7 @V4:VA=88 A?04:>28<8
70E2>@N20==O<8, ?>2'O70=8<8 7 =5?5@5=>A878.
5B8;?0@015= B0 ?@>?V;?0@015= <>6CBL A?@8G8=OB8 0;5@3VG=V @50:FVW (<>6;82>,
2V4AB@>G5=V C G0AV).

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

03VB=VABL. ;V=VG=V 40=V I>4> 70AB>AC20==O F5B8@878=C C ?5@V>4 203VB=>ABV 4C65 >1
<565=V. 0=V 4>A;V465=L =0 B20@8=0E =5 2:07CNBL =0 =0O2=VABL ?@G>3> 01> =5?@O<>3>
H:V4;82>3> 2?;82C FL>3> 70A>1C =0 ?5@51V3 203VB=>ABV, @>728B>: 5<1@V>=0/?;>40, ?>;>38 01>
?>AB=0B0;L=89 @>728B>:.
5@V>4 3>4C20==O 3@C44N. # 203VB=8E 6V=>: 01> C 6V=>:, O:V 3>4CNBL 3@C44N, F59 ?@5?0@0B
A;V4 70AB>A>2C20B8 7 >15@56=VABN, >A:V;L:8 F5B8@878= ?@>=8:0T C 3@C4=5<>;>:.

**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.**

E>4V >1T:B82=8E 28ABV :5@C20B8 B@0=A?>@B=8<8 70A>10<8, ;0B5=B=>3> ?5@V>4C A=C B0
?@>4C:B82=>ABV ?@0FV =0 :>=25T@=V9 ;V=VW A;:040==O =5 1C;> 28O2;5=> 6>4=8E ;;V=VG=>
7=0GC18E 5D5:BV2 ?@8 70AB>AC20==V @5:><5=4>20=>W 4>78 10 <3.
0FVT=B8, O:V ?;0=CNBL :5@C20B8 B@0=A?>@B=8<8 70A>10<8, 709<0B8AO ?>B5=V9=>
=5157?5G=8<8 2840<8 4VO;L=>ABV 01> ?@0FN20B8 7 <5E0=V7<0<8, <0NBL =5 ?5@528IC20B8 @5:>
<5=4>20=C 4>7C V 2@0E>2C20B8 A2>N 2V4?>2V4L =0 40=89 ?@5?0@0B. # GCB;828E ?0FVT=BV2 =0
B;V >4=>G0A=>3> 70AB>AC20==O FL>3> ?@5?0@0BC 7 0;>3>;5< 01> V=H8<8 45?@5A0=B0<8
F5=B@0;L=>W =5@2>2>W A8AB5<8 (&!)<>65 28=8:0B8 4>40B:>25 7=865==O :>=F5=B@0FVW C2038
B0 0:B82=>ABV.

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

=AB@C:FVW I>4> @>7:@8BBO D;0:>=0 V7 70E8A=8< :>2?0G:>< B0 I>4> 2V478.

1. 5B5;L=> AB@CA8B8 D;0:>= 7 A8@>?>< (?@>4>26 1;87L:> 5 A5:C=4).
2. \$;0:>=8 28?CA:0NBLAO 7 :>2?0G:>< 7 DC=:FVTN 70E8ABC 2V4 @>7?5G0BC20==O 4VBL<8.)>1
2V4:@8B8, =5>1EV4=> A8;L=> =0B8A=CB8 =0 :>2?0G>: C =0?@O25@=CB8 9>3> ?@>B8 3>48==8:>2>W
AB@V;:8.
3. @>AC=CB8 @;5G:> D;0:>=0 4> 70=C@5==O C A8@>?. 5 B@510 ?5@525@B0B8 D;0:>=.
4. 01@0B8 4>7C A8@>?C 70 4>?>>3>N ?>@H=O W ?V?5B:8 (2V4?>2V4=> 4> :0;V1@C20;L=8E : =0
?V?5BFV 2 <);.
5. 8BO3=CB8 @;5G:0 D;0:>=0.
6. 0B8 48B8=V 28?8B8 A8@>?, ?>B B0 ?;02=> =0B8A=C2H8 =0 ?>@H5=L 01> =0;82H8 A8@>? 7 ?V?5B:8
2 G09=C ;>6:C V =0?>W2H8 7 =5W 48B8=C.
7. VA;O 28:>@8AB0==O 7=>2C IV;L=> 70:@CB8B8 :>2?0G>: D;0:>=0.@><8B8 N 2>4>N B0 70;8H8B8
4;O 28A8E0==O.
>7C20==O.

VB8 2V:>< 2V4 2 4> 6 @>:V2: ?> 2,5 <3 F5B8@878=C 42VGV =0 4>1C (?> 2,5 <; A8@>?C 42VGV =0 4>1C).

VB8 2V:>< 2V4 6 4> 12 @>:V2: ?> 5 <3 F5B8@878=C 42VGV =0 4>1C (?> 5 <; A8@>?C 42VGV =0 4>1C). >@>A;V B0 ?V4;VB:8 2V:>< 2V4 12 @>:V2: ?> 10 <3 F5B8@878=C 1 @07 =0 4>1C (?> 10 <; A8@>?C 1 @07 =0 4>1C).

!8@>? <>6=0 :>2B0B8 157 @>72545==O.

0FVT=B8 ;VB=L>3> 2V:C: 4>ABC?=V 40=V =5 2:07CNBL =0 =5>1EV4=VABL 7<5=H5==O 4>78 C >AV1 ;VB=L>3> 2V:C 70 C<>28 =>@<0;L=>W DC=:FVW =8@>:.

0FVT=B8 7 ?>N 01> BO6:>N =8@>:2>N =54>AB0B=VABN: 4>:C<5=B0;L=> ?V4B25@465=V 40=V I>4> A?V22V4=>H5==O 5D5:B82=>ABV V 157?5G=>ABV C ?0FVT=BV2 7 =8@>:2>N =54>AB0B=VABN 2V4ACB=V. A:V;L:8 F5B8@878= 5:A:@5BCTBLAO 2 >A=>2=>74V; «\$0@<0;>;>3VG=V 2;0AB82>ABV», C 28?04:0E 2V4ACB=>ABV 0;LB5@=0B82=>W B5@0?VW F59 ?@5?0@0B <>65 70AB>A>2C20B8AO C 40=V9 ?>?C;OFVW, 0;5 70 C<>28 V=482V4C0;L=>W :>@5:FVW V=B5@20;V2 ?@89>1EV4=> 2V4:>@83C20B8 4>7C 2V4?>2V4=> 4> V=D>@<0FVW, ?@54AB02;5=>W C B01;8FV =86G5. ;O @>7@0EC=:C 2V4:>@83>20=>W 4>78 =5>1EV4=> 7=0B8 @>7@0E>20=5 7=0G5==O ;;V@5=AC :@50B8=V=C ?0FVT=B0 (:@) C <;/E2. =0G5==O :@ (<;/E2) <>65 1CB8 @>7@0E>20=5 =0 >A=>2V @57C;LB0BV2 287=0G5==O 220B:>2>3> :@50B8=V=C (<3/4;) 70 =0ABC?=>N D>@N:

:@ = [140 - 2V: (@>:V2)] x <0A0 BV;0 (:3) (x 0,85 4;O 6V=>:)

72 x :@50B8=V = A8@>20B:8 :@>2V (<3/4;)

>@83C20==O 4>78 C 4>@>A;8E ?0FVT=BV2 7 =8@>:2>N =54>AB0B=VABN.

@C?0	;V@5=A :@50B8=V=C (<; /E2)	>70 B0 :@0B=VABL ?@89>
>@<0;L=0 DC=:FVO =8@>:	≥ 80	10 <3 F5B8@878=C 1 @07 =0 4>1C
53:0 =8@>:20 =54>AB0B=VABL	50 79	10 <3 F5B8@878=C 1 @07 =0 4>1C
>20 =54>AB0B=VABL	30 49	5 <3 F5B8@878=C 1 @07 =0 4>1C
"06:0 =8@>:20 =54>AB0B=VABL	< 30	10 <3 F5B8@878=C 1 @07 :>6=V 2 4>18
"5@@N20==O =8@>: ?0FVT=B8 =0 4V0;V7V	< 10	@5?0@0B ?@>B8?>:070=89

?54V0B@8G=8E ?0FVT=BV2 V7 =8@>:2>N =54>AB0B=VABN 4>7C :>@83CNBL =0 V=482V4C0;L=V9 >A=>2V 7 C@0EC20==O <?>:07=8:V2 =8@>:2>3> ;;V@5=AC, 2V:C B0<0A8 BV;0 ?0FVT=B0.

0FVT=B8 7 ?5GV=:>2>N =54>AB0B=VABN: C ?0FVT=BV2 ;8H5 7 ?5GV=:>2>N =54>AB0B=VABN :>@83C20==O 4>78 =5 ?>B@V1=>.

0FVT=B8 7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 B0 =8@>: :@5:><5=4CTBLAO 2V4:>@83C20B8 4>7C (482. ?V4@>74V; «0FVT=B8 7 ?>N 01> BO6:>N =8@>:2>N =54>AB0B=VABN», =02545=89 2815).

VB8.

@5?0@0B ?@87=0G0B8 4VBO< 2V:>< 2V4 2 @>:V2.

5@54>7C20==O.

!8<8. !8<8, O:V A?>AB5@V30;8AO ?VA;O ?5@54>7C20==O F5B8@878=C, 1C;8 0A>FV9>20=V 2 >A=>2=>

>2V4><;O;>AO, I> ?VA;O 70AB>AC20==O 4>78, O:0 I>=09<5=H5 C 5 @07V2 ?5@528ICT @5:> <5=4>20=C 4>1>2C 4>7C, 28=8:0;8 =0ABC?=V =51060=V O28I0: A?;CB0=VABL A2V4>>ABV, 4V0@50, 70?0<>@>G5==O, 2B><;N20=VABL, 3>;>2=89 1V;L, 7030;L=5 =574C60==O;V9, A540B82=89 5D5:B, A>;82VABL, ABC?>@, B0EV:0@4VO, B@5>@ B0 70B@8282545==O.

V:C20==O. □V4><>3> A?5F8DVG=>3> 0=B84>BC 4> F5B8@878=C =5 VA=CT.

@8 ?5@54>7C20==V @5:><5=4CTBLAO A8<0B8G=0 B0 ?V4B@8<820==O H;C=:0 4>FV;L=5, O:I> =0470 ?@5?0@0BC 1C;0 70AB>A>20=0 =5I>402=>.

V0;V7 T =55D5:B82=8< 4;O 282545==O F5B8@878=C 7 >@30=V7

>1VG=V @50:FVW.

:V=VG=V 4>A;V465==O ?>:070;8, I> F5B8@878= ?@8 70AB>AC20==V C @5:<>5=4>20=8E 4>70E <OT
=57=0G=89 ?>1VG=89 2?;82 =0 F5=B@0;L=C =5@2>2C A8AB5 2.;NG0T A>;82VABL, ?V428I5=C 2B>
<;N20=VABL, 70?0<>@>G5==O B0 3>;>2=89 1V;L. # 45O:8E 28?04:0E ?>2V4<;O;>AO ?@>
?0@04>:A0;L=C AB8W =5@2>2>W A8AB5<8.

5B8;?0@03V4@>:A815=7>0B B0 ?@>?V;?0@03V4@>:A815=7>0B, I> 2E>4OBL 4> A.;04C A8@>?C,
<>6CBL A?@8G8=OB8 @>728B>: 0;5@3VG=8E @50:FV9 (<>6;82>, 2V4AB@>G5=8E).

%>G0 F5B8@878= T A5;5:B82=8< 0=B03>=VAB< ?5@8D5@8G=8E H1-@5F5?B>@V2 B0 <0965 =5
G8=8BL 0=B8E>;8=5@3VG=>W 4VW, ?>2V4<;O;>AO ?@> ?>>48=>:V 28?04:8 28=8:=5==O
CB@C4=5==O A5G>28?CA:0==O, ?>@CH5==O 0:<>40FVW >:0, ACE>ABV C @>BV.

>2V4<;O;>AO ?@> 28?04:8 ?>@CH5==O DC=:FV9 ?5GV=:8, I> E0@0:B5@87C20;8AO ?V428I5=8<8
@V2=O<8 D5@<5=BV2 ?5GV=:8, O:V AC?@>2>46C20;8AO ?V428I5=8< @V2=5< 1V;V@C1V=C.

0728G09 AB0= =>@<0;V7C202AO ?VA;O ?@8?8=5==O 70AB>AC20==O ?@5?0@0BC.

:;V=VG=8E 4>A;V465==OE 7 ?>:07=8:<< 1 % B0 28I5 ?>2V4<;O;>AO ?@> =0ABC?=V ?>1VG=V
5D5:B8:

7030;L=V ?>@CH5==O ?V428I5=0 2B><;N20=VABL;

7 1>:C =5@2>2>W A8AB5<8 70?0<>@>G5==O, 3>;>2=89 1V;L;

7 1>:C H;C=:>2>-:8H:>2>3> B@0:BC 014>BV, =C4>B0;

7 1>:C ?A8EV:8 A>;82VABL;

7 1>:C 48E0;L=>W A8AB5<8 D0@8=3VB.

>1VG=V 5D5:B8, I> A?>AB5@V30;8AO 7 ?>:07=8:<< 1 % B0 28I5 C ?;0F51>-:>=B@>;L>20=8E

4>A;V465==OE C 4VB59 2V:<< 2V4 6 12 @>:V2:

7 1>:C H;C=:>2>-:8H:>2>3> B@0:BC 4V0@5O;

7 1>:C ?A8EV:8 A>;82VABL;

7 1>:C 48E0;L=>W A8AB5<8 @8=VB;

7030;L=V ?>@CH5==O ?V428I5=0 2B><;N20=VABL.

>AB<0@:5B8=3>2V A?>AB5@565==O.

>1VG=V 5D5:B8 2:070=V 73V4=> 7 !(:;0AC A8AB5<8 >@30=V2) 70 MedDRA B0 70 G0AB>B>N, 7 O:>N
2>=8 A?>AB5@V30;8AO 2?@>4>26 ?>AB<0@:5B8=3>2>3> A?>AB5@565==O.

'0AB>B0 287=0G5=0 O: =0ABC?=0: 4C65 G0AB> (>=1/10); G0AB> (2V4 >=1/100 4> <1/10); =5G0AB> (2V4
>=1/1000 4> <1/100); @V4:> (2V4 >=1/10000 4> <1/1000); 4C65 @V4:> (<1/10000), =52V4><> (=5<>6;82>
2AB0=>28B8 7 VA=CNG8E 40=8E).

1AB565==O: @V4:> 71V;LH5==O <0A8 BV;0.

I>:C A5@FO: @V4:> B0EV:0@4VO.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 4C65 @V4:> B@><1>F8B>?5=VO.

I>:C =5@2>2>W A8AB5<8: =5G0AB> ?0@5AB57VO; @V4:> AC4><8; 4C65 @V4:> 48A3527VO,

48A:V=57VO, 48AB>=VO, =5?@8B><=VABL, B@5<>@; G0AB>B0 =52V4><0 0<=57VO, ?>@CH5==O ?0
<□OBV.

I>:C >@30=V2 7>@C: 4C65 @V4:> ?>@CH5==O 0:<>40FVW, =5GVB:VABL 7>@C,<8<>2V;L=V
@CE8 >G=>3> O1;C:0.

I>:C >@30=V2 A;CEC B0 @V2=>2038: 25@B83>.

I>:C H;C=:>2>-:8H:>2>3> B@0:BC: =5G0AB> 4V0@5O.

I>:C =8@>: B0 A5G>282V4=>W A8AB5<8: 4C65 @V4:> 487C@VO, 5=C@57; G0AB>B0 =52V4><0
70B@8

I>:C H:V@8 B0 ?V4H:V@=>W :;VB:>28=8: =5G0AB> A25@1V6, 28A8?0==O; @V4:> :@>?82O=0; 4C65
@V4:> 0=3V>=52@>B8G=89 =01@O.;

030;L=V ?>@CH5==O: =5G0AB> 0AB5=VO, =574C60==O; @V4:> =01@O:.

I>:C VW A8AB5<8: @V4:> 3V?5@GCB;82VABL; 4C65 @V4:> 0=0DV;0:B8G=89 H>;: =52V4><>
0;5@3VG=V @50:FVW (<>6;82>, 2V4AB@>G5=V C G0AV).

I>:C 35?0B>1V;V0@=>W A8AB5<8: @V4:> ?>@CH5==O DC=:FV9 ?5GV=:8 (?V428I5==O @V2=O
B@0=A0W D>AD0B078, γ- 3;CB0).

I>:C ?A8EV:8: =5G0AB> B@82>6=VABL; @V4:> 03@5A82=VABL, A?;CB0=VABL A2V4>>ABV,
45?@5AVO, 30;NF8=0FVW, 157A>==O; 4C65 @V4:> BV.; G0AB>B0 =52V4><0 ACWF840;L=V 4C

I>:C E0@GC20==O B0 >128=: G0AB>B0 =52V4><0 ?V428I5=89 0?5B8B.

"5@ABV.3 @>:8.

#<>28 715@V30==O.

5 ?>B@51CT A?5FV0;L=8E C<>2 715@V30==O. 15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 100 <; A8@>?C C D;0:>=V V7 70E8A=>N :@8H:>N, ?> 1 D;0:>=C @07< V7 N ?V?5B:>N C :0@B>==V9
:>@>1FV.

0B53>@VO 2V4?CA:C. 57 @5F5?B0.

8@>1=8:.

"«5=BV20».

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

:015;>2=8 130, 102 37 @030 10, >;=V TE>;C?8, '5AL:0 5A?C1;V:0.