

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

0;357V=®
(NALGESIN®)

!;:04 ;V:0@AL:>3> 70A>1C:

4VNG0 @5G>28=0: =0?@>:A5= =0B@VN;

1 B01;5B:0, 2:@8B0 ?;V2:>2>N >1>;>=:>N,

4>?>28=8: ?>2V4=>, F5;N;>70 :@8AB0;VG=0, B0;L:, <03=VN AB50@0B, 3V?@><5;>70, B8B0=C

4V>:A84 (171), <0:@>3>;, V=483>:0@.

V:0@AL:0 D>@<0.

"01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N.

20;L=V, 7;53:0 42>>?C:;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 1;0:8B=>3> :>;L>@C.

0720 V 465==O 28@>1=8:0.

, 4.4., >2> <5AB>, !;>25=VO.

(<0@TH:0 F5AB0 6, 8501 >2> <5AB>, !;>25=VO/

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\$0@<0:>B5@0?52B8G=0 3@C?0. 5AB5@>W4=V ?@>B870?0;L=V B0 ?@>B8@52<0B8G=V 70A>18.

>EV4=V ?@>?V=>=>2>W :8A;>B8. 0?@>:A5=. >4 " ! 0102.

0?@>:A5= =0B@VN =5AB5@>W4=89 ?@>B870?0;L=89 70AV1. '8=8BL 7=51>;N20;L=C, ?@>B870?0;L=C

B0 60@>7=86C20;L=C 4VN. 5E0=V7< 4VW ?@5?0@0BC >1C<>2;5=89 ?@83=VG5==O<

F8:;>>:A835=078, D5@<5=BC, O:89 15@5 CG0ABL C A8=B57V ?@>AB03;0=48=V2. =0A;V4>: FL>3>

7=86CNBLAO @V2=V ?@>AB03;0=48=V2 2 @V7=8E @V48=0E B0 B:0=8=0E >@30=V7

VA;O ?5@>@0;L=>3> 70AB>AC20==O =0?@>:A5==0B@VN 4C65 H284:> 3V4@>;V7CTBLAO 2

:8A;>B=>2>:C. 82V;L=NNBLAO G0AB:8 =0?@>:A5=C, O:V ?>BV< C B>=:V9 :8HFV 4C65 H284:>

@>7G8=ONBLAO. &5 ?@872>48BL 4> 1V;LH H284:>W B0 ?>2=>W 01A>@1FVW =0?@>:A5=C.

0:A8<0;L=0 :>=F5=B@0FV0 2 ?;07AB5@V30TBLAO G5@57 1-2 3>48=8 ?VA;O ?@89>V2=V

=0?@>:A5=C 2 ?;07?>@FV9=> 4> @>77 4> 500 <3. @8 1V;LH8E 4>70E 2>=8 <5=H ?@>?>@FV9=V.

;87L:> 99 % =0?@>:A5=C 72O7CTBLAO 7 0;L1C

@81;87=> 70 % =0?@>:A5=C 282>48BLAO C =57 30 % C 283;O4V =50:B82=>3> <5B01>;VBC 6-48<5B8;-

=0?@>:A5=C. @81;87=> 95 % ?@5?0@0BC 282>48BLAO 7 A5G5N B0 5 % 7 D5:0;VO<8. V;>;>3VG=89

?5@V>4 =0?V2282545==O =0?@>:A5=C =5 70;568BL 2V4 :>=F5=B@0FVW 2 ?;0778 V AB0=>28BL 1215

3>48=.

>:070==O 4;O 70AB>AC20==O.

0;357V=® 70AB>A>2CTBLAO:

?@8 7C1=>;>2=>;N;

?@8 1>;N 2 <O70E, AC3;>10E B0 E@51BV;

4;O 70?>1V30==O ;53H5==O;

?@8 <5=AB@C0;L=>;N.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> =0?@>:A5=C =0B@VN G8 4> 1C4L-O:>W 4>?>W @5G>28=8.

V428I5=0 GCB;82VABL 4> A0;VF8;0BV2 B0 V=H8E =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2, I>

?@>O2;OTBLAO C 283;O4V 1@>=EV0;L=>W 0AB<8, :@>?82O=:8 B0 =070;L=8E ?>;V?V2.

>AB@89 ?5@V>4 G8 @5F8482 28@07:8 H;C=:0 G8 420=04FOB8?0;>W :8H:8, :@>2>28;828 2 (".

"O6:V ?>@CH5==O DC=:FVW ?5GV=:8 B0 =8@>: (;V@5=A :@50B8=V=C <5=H5 30 <;/E2).

!5@F520 =54>AB0B=VABL.

03VB=VABL B0 3>4C20==O 3@C44N.

V: 4> 16 @>:V2.

0;56=V 70E>48 157?5:8 ?@8 70AB>AC20==V.

0FVT=B0< V7 70E2>@N20==O<8 H;C=:>2>:-8H:>2>3> B@0:BC, >A>1;82> 7 28@07:>28< :>;VB<< G8 E2>@>1>N @>=0 (B0:>6 C <8=C;>
/: V C 28?04:C 7 V=H8<8 =5AB5@>W4=8<8 ?@>B870?0;L=8<8 70A>10<8, AC<0@=0 G0AB>B0 ?>O28 A5@9>7=8E ?>1VG=8E O28I, :@>2>B5GV B0 ?5@D>@0FVW 2 H;C=:>2>:-8H:>2> 7 B@820;VABN ;V:C20==O. @89< 1V;LH8E 4>7 =0?@>:A5=C B0:>6 <>65 71V;LH8B8 @878: ?>O28 ?>1VG=8E 5D5:BV2. # @07V B@820;>3> 70AB>AC20==O =5>1EV4=89 ?>ABV9=89 =03;O4 7 <5B>N 28O2;5==O ?>1VG=8E @50:FV9. N48 ;VB=L>3> 2V:C B0 >A;01;5=V ?0FVT=B8 1V;LH AE8;L=V 4> CB2>@5==O H;C=:>2>:-8H:>28E 28@07>:, :@>2>B5G B0 @>728B:C A5@9>7=8E ?>1VG=8E @50:FV9. # >AV1, 2 0=0<=57V O:8E T 1@>=EV0;L=0 0AB<0, 0;5@3VG=V 70E2>@N20==O 01> 28?04:8 1@>=E>A?076CBL A?>AB5@V30B8AO 2V4E8;5==O ;01>@0B>@=8E B5ABV2 DC=:FVW ?5GV=:8. 0?@>:A5= 7<5=HCT 03@530FVN B@<<1>F8BV2 B0 ?>4>26CT G0A :@>2>B5GV. &5 ?>B@V1=> 1@0B8 4> C2038 ?@8 287=0G5==V G0AC :@>2>B5GV. @8 70AB>AC20==V =0?@>:A5=C <>6;8289 =57=0G=89 ?5@8D5@8G=89 =01@O:, 1V;LH89 @878: 9>3> @>728B:C C E2>@8E 7 ?>@CH5==O< DC=:FVW A5@FO. 0FVT=B8 V7 ?>@CH5==O< 73>@B0==O :@>2V B0 ?0FVT=B8, O:V 70AB>A>2CNBL ?@5?0@0B8, I> 2?;820NBL =0 35<>AB07, ?>B@51CNBL >A>1;82>3> =03;O4C. # @07V >4=>G0A=>3> 70AB>AC20==O 0=B8:>03C;O=BV2 ?V428ICTBLAO @878: :@>2>B5G. =0DV;0:B>W4=V (0=0DV;0:B8G=V) @50:FVW <>6CBL 28=8:0B8 C >AV1 O: V7 =0O2=VABN 2 0=0 <=57V @50:FV9 3V?5@GCB;82>ABV 4> 0A?V@8=C, V=H8E 01> 70A>1V2, I> :A5=, B0: V 157 =8E. # ?0FVT=BV2, 2 0=0<=57V O:8E T 0=3V>545<0, 1@>=E>A?07<, 0AB<0, @8=VB8 B0 =>A>2V ?>;V?8, B0:>6 <>6CBL @>72820B8AL 0=0DV;0:B>W4=V @50:FVW. 5O:V 7 =8E, =0?@8;;04 0=0DV;0:B8G=89 H>; <>6CBL <0B8 ;5B0;L=89 =0A;V4>:.

28?04:C 7<5=H5==O 4>78 01> 6 2V4W4=8E ;V:0@AL:8E 70A>1V2 ?V4 G0A B5@0?VW =0?@>:A5=<, WE 4>7C A;V4 7<5=HC20B8 ?>ABC?>2> B0 ?V4 ?8;L=8< =03;O4<< ;V:0@O 4;O 28O2;5==O 1C4L-O:8E ?>1VG=8E @50:FV9, 2;;NG0NG8 =54>AB0B=VABL :>@8 =04=8@:>2>W 70;>78 B0 703>AB@5==O A8 @8 70AB>AC20==V , 2;;NG0NG8 =0?@>:A5=, 7@V4:0 A?>AB5@V30;8AL 70E2>@N20==O >G59, 7>:@5 <0 ?0?V;VB, @5B@>1C;L10@=89 =52@8B B0 =01@O: A>A>G:0 7>@>2>3> =5@20, E>G0 ?@8G8==> =0A;V4:>289 72?O7>: 2AB0=>2;5=> =5 1C;>. '5@57 F5 ?0FVT=B0<, C O:8E @>72820NBLAO ?>@CH5==O 7>@C ?V4 G0A ;V:C20==O =0?@>:A5=<, ?>B@V1=> ?@>E>48B8 >DB0;L<>;>3VG=5 >1AB565==O. > ?>G0B:C ;V:C20==O =0?@>:A5=< =5>1EV4=> 7OAC20B8 (15AV40 7 ;V:0@5-) =0O2=VABL 2 VAB>@VW E2>@>18 ?0FVT=B0 3V?5@B5=7VW B0/01> A5@F52>W =54>AB0B=>ABV V7 70B@8N @V48=8 B0 =01@O:0<8, 0A>FV9>20=8<8 7 ?@89><<< . 8E>4OG8 7 ;;V=VG=8E 4>A;V465=L B0 5?V45;>3VG=8E 40=8E ?@8?CA:0NBL, I> 7@>AB0==O @878:C 0@B5@V0;L=>3> B@<1>7C <>65 1CB8 ?>2O70=5 V7 70AB>AC20==O< 45O:8E (>A>1;82> C 28A>:8E 4>70E B0 4>2389 G0A). 3V4=> 7 F8<8 40=8<8, 26820==O =0?@>:A5=C (1000 <3 =0 45=L) ?>2O70=5 V7 <5=H8<8 @878:0<8, ?@>B5 45O:V @878:8 =5 <>6CBL 1CB8 28;;NG5=V. 5<0T 4>AB0B=VE 40=8E ?@> 70AB>AC20==O =87L:8E 4>7 =0?@>:A5=C =0B@VN, =0?@8;;04 275 <3, 4;O 28A=>2:V2 I>4> @878:C B@<<1>7C.

;O ?0FVT=BV2 V7 =5>=B@>;L>20=>N 0@B5@V0;L=>N 3V?5@B5=7VTN, 70ABV9=>N A5@F52>N =54>AB0B=VABN, VH5N E2>@>1>N A5@FO, E2>@>1>N ?5@8D5@8G=8E 0@B5@V9 B0/01> ?>@CH5==O< <>7:>2>3> :@>2>>1V3C A;V4 @5B5;L=> 72068B8 =5>1EV4=VABL 70AB>AC20==O =0?@>:A5=C. ;O >AV1 V7 D0:B>@0<8 @878:C 28=8:=5==O A5@F52>-AC48==8E ?>4V9 (=0?@8;;04 3V?5@B5=7VO, 3V?5@>;V?V456 @5B5;L=> 72068B8 =5>1EV4=VABL 70AB>AC20==O =0?@>:A5=C ?5@54 ?>G0B:<< 4>23>B@820;>W B5@0?VW. 0?@>:A5=, O: V V=HV V=3V1VB>@8 A8=B57C F8;;>:A835=078, <>6CBL 2?;820B8 =0 D5@B8;L=VABL. V=:0<, O:V =0<030NBLAO 70203VB=VB8 B0/01> <0NBL ?@>1;5<8 V7 70G0BB0<, A;V4 ?@8?8=8B8 70AB>A>2C20==O =0?@>:A5=C.

A>1;82V 70AB5@565==O.

V=V1VG=8E @50:FV9 <>6=0 4>AO3B8 H;OE<< 70AB>AC20==O =09=86G8E 5D5:B82=8E 4>7 B0 7 <5=H5==O B@820;>ABV ?@89> 0 =0O2=>ABV V=D5:FV9=>3> 70E2>@N20==O A;V4 2@0E>2C20B8 ?@>B870?0;L=V B0 60@>7=86C20;L=V 5D5:B8 =0?@>:A5=C 2>=8 <>6CBL <0A:C20B8 >7=0:8 F8E 70E2>@N20=L.

0?@>:A5= B0 9>3> <5B01>;VB8 3>;>2=8< G8=>< 282>4OBLAO =8@:0<8 H;OE<< ;C1>G:>2>W
DV;LB@0FVW, B>A5= =0B@VN A;V4 4C65 >15@56=> ?@87=0G0B8 ?0FVT=B0< 7 ?>@CH5==O<8
DC=:FVW =8@>.: 0FVT=B0< 7 =8@:>2>N =54>AB0B=VABN A;V4 287=0G8B8 ;V@5=A :@50B8=V=C B0
:>=B@>;N20B8 9>3> ?@>B03>< ;V:C20==O. 5 @5:><5=4CTBLAO ?@89>< =0?@>:A5=C, O:I> ;V@5=A
:@50B8=V=C <5=H89 =V6 20 <;/E2 (0,33 <;/A).

A>1;82> A;V4 70AB5@53B8 ?0FVT=BV2 7 ?>@CH5==O<8 DC=:FVW ?5GV=:8. @8 E@>=VG=>3>;L=>
7V ?5GV=:8 B0, <>6;82>, ?@8 V=H8E D>@<0E F8@>7C 7030;L=V :=F5=B@0FVW =0?@>:A5=C
=0B@VN 2 ?;07<5=4CTBLAO ?@89>< =09<5=H8E 5D5:B82=8E 4>7.

V:0@N A;V4 C206=> A?>AB5@V30B8 70 ?0FVT=B0<8 7 5?V;5?AVTN G8 ?>@DV@VTN, O:V ?@89
<0NBL =0?@>:A5=.

0FVT=B8 ;VB=L>3> 2V:C ?>28==V ?@89<0B8 0;357V=® 2 =09<5=H8E 5D5:B82=8E 4>70E.

06:820 V=D>@<0FVO ?@> 45O:V V=3@54VT=B8 0;357V=C®

V:0@AL:89 70AV1;L>2>W 4VTB8.

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

0AB>AC20==O 0;357V=C® 2 ?5@V>4 203VB=>ABV ?@>B8?>:070=>.

0 =5>1EV4=>ABV 70AB>AC20==O 0;357V=C® C ?5@V>4 3>4C20==O 3@C44N, 3>4C20==O
=5>1EV4=> ?@8?8=8B8.

**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.**

V4 G0A 70AB>AC20==O 0;357V=C® 45O:V ?0FVT=B8 <>6CBL 2V4GC20B8 A>;82VABL, 70?0
<>@>G5==O, 25@B83>, @>7;048 7>@C, 157A>==O 01> 45?@5AVN, I><>65 2?;820B8 =0 H284:VABL
@50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B<< B0 @>1>BV 7 V=H8<8 <5E0=V7<0<8.

VB8.

0;357V=® ?@>B8?>:070=89 4VBO< 4> 16 @>:V2.

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

"01;5B:8 A;V4 :>2B0B8 FV;8<8, 70?820NG8 A;;O=:>N 2>48. V:C20==O A;V4 @>7?>G8=0B8 7 =09=86G>W
@5:><5=4>20=>W 4>78.

>@>A;V B0 4VB8 2V4 16 @>:V2

CI=89 IV;L, 3>;>2=89 IV;L, 1V;L C<O70E, AC3;>10E B0 E@51BV.

5:><5=4>20=0 4>70 2 B01;5B:8 (550 <3) 42VGV =0 45=L, 0;5 =5 1V;LH5 =V6 4 B01;5B:8 (1100 <3) =0
45=L. 0 28=OB:>< A8;L=>3> 1>;N (>:@V< 70E2>@N20==O A:5;5B=>-<O7>2>W B:0=8=8), 70 O:>3>
<>6;82> 71V;LH8B8 4>7C 4> 5 B01;5B>: =0 45=L (1375 <3).

V3@5=L

@8 ?5@H8E >7=0:0E =0?04C @5:><5=4>20=0 ?>G0B:>20 4>70 AB0=>28BL 3 B01;5B:8 (825 <3). 0
=5>1EV4=>ABV, 1 B01;5B:C (275 <3) 01> 2 B01;5B:8 <>6=0 1CB8 ?@89=OB8 4>40B:>2>, 0;5 =5 @0=VH5
=V6 G5@57 ?V23>48=8 ?VA;O ?@89=OBBO ?>G0B:>2>W 4>78. >1>20 4>70 =5<0T ?5@528IC20B8 5
B01;5B>: =0 45=L (1375 <3).

5=AB@C0;L=89 IV;L

5:><5=4>20=0 ?>G0B:>20 4>70 2 B01;5B:8 (550 <3), 70 =5>1EV4=>ABV <>6=0 ?@89<0B8 ?> 1 B01;5BFV
(275 <3) :>6=V 6-8 3>48=. 0:A8<0;L=0 4>70 AB0=>28BL 5 B01;5B>: (1375 <3) C ?5@H89 45=L ?@89>
"@820;VABL ?@89>;53H5==O 1>;N AB0=>28BL 10 4=V2.

/:I> A8<8 =5 7=8:0NBL, A;V4 ?@>:=AC;LBC20B8AL V7 ;V:0@5

N48 ?>E8;>3> 2V:C

0;357V=® A;V4 70AB>A>2C20B8 C =09=86G8E 5D5:B82=8E 4>70E.

0FVT=B8 2V:<< ?>=04 65 @>:V2 ?>28==V ?@89<0B8 B01;5B:8 =5 G0ABVH5 =V6 G5@57 12 3>48=, O:I>
F5 =5>1EV4=>.

0FVT=B8 7 ?>@CH5==O< DC=:FVW =8@>:

0;357V=® A;V4 70AB>A>2C20B8 C =09=86G8E 5D5:B82=8E 4>70E.

0FVT=B8 7 ?5GV=:>2>N =54>AB0B=VABN

0;357V=® A;V4 70AB>A>2C20B8 C =09=86G8E 5D5:B82=8E 4>70E.

5@54>7C20==O.

VA;O 28?04:>2>3> G8 =02<8A=>3> ?@89>W :V;L:>ABV =0?@>:A5=C =0B@VN <>65 7O28B8AO 1V;L C G5@52=V9 ?>@>6=8=V, =C4>B0, 1;N20==O, 70?0<>@>G5==O, 472V= C 2CE0E, @>74@0B>20=VABL, C 1V;LH BO6:8E 28?04:0E B0:>6 <>65 7O28B8AO :@82025 1;N20==O, <5;5=0, ?>@CH5==O A2V4<>>ABV, 48E0;L=V @>7;048, AC4<>8 B0 =8@>:20 =54>AB0B=VABL. >:070=> B0:5 ;V:C20==O: ?@>820==O H;C=:0, 0:B82>20=5 2C3V;;O, 0=B0F848, V=3V1VB>@8 H2-@5F5?B>@V2, V=3V1VB>@8 ?@>B>==>W ?>?@>AB>; B0 V=HV D>@<8 A8<0B8G=>3> ;V:C20==O.

>1VG=V 5D5:B8.

I>:C A8AB5<8 :@>2>B2>@5==O B0 ;VW A8AB5<8: 5>78=>DV;VO, 3@0=C;>F8B>?5=VO, ;59:>?5=VO, B@><1>F8B>?5=VO, 0?;0AB8G=0 0=5, 03@0=C;>F8B>7.

I>:C VW A8AB5<8: @50:FVO 3V?5@GCB;82>ABV, 0=0DV;0:B8G=V @50:FVW.

I>:C ?A8EV:8: AC4<>8, 0=><0;L=V A=>284V==O.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 25@B83>, 70?0<>@>G5==O, A>=;82VABL, 45?@5AVO, ?>@CH5==O A=C, =5740B=VABL 7>A5@548B8AL, 157A>==O, A;01:VABL0A5?B8G=89 <5=V=3VB, :>3=VB82=V @>7;048.

I>:C >@30=V2 7>@C: ?>@CH5==O 7>@C, ?>3V2:8, ?0?V;VB, @5B@>1C;L10@=89 =52@8B, =01@O: A>A>G:0 7>@>2>3> =5@20.

I>:C >@30=V2 A;CEC B0 ;01V@8=BC: HC< C 2CE0E, ?>@CH5==O A;CEC, ?>3V@H5==O A;CEC.

I>:C A5@FO: =01@O.; 2V4GCBBO A5@F518BBO, 70ABV9=0 A5@F520 =54>AB0B=VABL.

I>:C AC48=: 20A:C;VB.

I>:C 48E0;L=>W A8AB5<8, >@30=V2 3@C4=>W ;;VB:8 B0 A5@54>ABV==O: 48A?=>5, 5>78=>DV;L=0 ?=52<>=VO, 0AB<0, =01@O: ;535=L.

I>:C >128= B0 E0@GC20==O: 3V?5@3;V:53;V:5

I>:C H;C=:>2>-.8H:>2>3> B@0:BC: 70?>@, 1V;L C 682>BV, =C4>B0, 48A?5?AVO, 4V0@5O, AB> <0B8B, H;C=:>2>-.8H:>2V :@>2>B5GV B0/01> ?5@D>@0FVO H;C=:0, 1;N20==O, 1;N20==O 7 :@>2N, <5;5=0, 28@07:>289 AB<>0B8B, CB2>@5==O H;C=:>2>-.8H:>28E 28@07>.; :>;VB, 57>D03VB, ?0=:@50B8B.

I>:C ?5GV=:8 B0 6>2G>282V4=8E H;OEV2: ?V428I5=89 @V25=L D5@<5=BV2 ?5GV=:8, 6>2BO=8FO, 35?0B8B.

I>:C A:5;5B=>-<07>2>W B0 A?>;CG=>W B:0=8=: 1V;L C <070E B0 <07>20 A;01:VABL.

I>:C =8@>: B0 A5G>282V4=8E H;OEV2: 3;>5@C;>=5D@8B, 35<0BC@VO, V=B5@AB8FV0;L=89 =5D@8B, =5D@>B8G=89 A8=4@<, ?>@CH5==O DC=:FVW =8@>.; =8@>:20 =54>AB0B=VABL, =5:@>7 =8@>:28E A>A>G:V2.

I>:C AB0B528E >@30=V2 B0 <>;>G=>W 70;>78: 157?;V440 C 6V=>:.

I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: A25@1V6, 28A8?0==O =0 H:V@V, A8=FV, ?C@?C@0, 0;>?5FVO, D>B>GCB;82V 45@<0B8B8, 2C7;>20 5@8B5<0, G5@2>=89 ?;5A:0B89 ;8H09, ?CABC;8, A8AB5<89 G5@2>=89 2>2G0.; 5?V45@<0;L=89 =5:@>;V7, ?>;V<>@D=0 5@8B5<0, @50:FVW A2VB;>GCB;82>ABV, AE>6V =0 E@>=VG=C 35<0B>?>@DV@VN B0 1C;L>7=89 5?V45@<>;V7, A8=4@< !BV25=A0 - 6>=A>=0, :@>?82O=:0.

030;L=V @>7;048 B0 @50:FVW C A?@030, ?VB;82VABL, ?>@CH5==O<5=AB@C0FV9, 3V?5@B5@ 7=>1 V 30@OG:0), 0=3V>=52@>B8G=89 =01@O:.

?;82 =0 @57C;LB0B8 ;01>@0B>@=8E B0 V=AB@C<5=B0;L=8E 4>A;V465=L: 3V?5@:0;VT >2V4<>;O;>AO ?@> =01@O:8, 3V?5@B5=7VN B0 A5@F52C =54>AB0B=VABL, ?>2O70=V V7 ?@89<><. 8E>4OG8 7 ;;V=VG=8E 4>A;V465=L B0 5?V45;>3VG=8E 40=8E ?@8?CA:0NBL, I> 7@>AB0==O @878:C 28?04:V2 0@B5@V0;L=>3> B@><1>7C (=0?@8:;04 V=D0@:B :0@40 01> V=AC;LB) <>65 1CB8 ?>2O70=5 V7 70AB>AC20==O< 45O:8E (>A>1;82> C 28A>:8E 4>70E B0 4>2389 G0A). @8 28=8=:5==V BO6:8E ?>1VG=8E @50:FV9 ;V:C20==O A;V4 ?@8?8=8B8.

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

5 @5:><5=4CTBLAO AC?CB=V9 ?@89<< 0F5B8;A0;VF8;>2>W :8A;>B8 B0 V=H8E =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2 G5@57 25;8:89 @878: ?>O28 ?>1VG=8E @50:FV9.

4=>G0A=5 70AB>AC20==O V7 0=B0F840<8 01> E>;5AB8@0< <>65 A?>2V;L=8B8 01A>@1FVN =0?@>:A5=C, B0 =5 2?;820T =0 9>3> :V;L:VABL.

4=>G0A=5 70AB>AC20==O V7 A5@F528<8 3;V:>7840<8 <>65 ?@8725AB8 4> 703>AB@5==O A5@F52>W =54>AB0B=>ABV, 7=865==O H284:>ABV ;;C1>G:>2>W DV;LB@0FVW B0 71V;LH8B8 @V25=L A5@F528E 3;V:>784V2 C :@>2V.

5 A;V4 70AB>A>2C20B8 =0?@>:A5= ?@>B03<< 8-12 4=V2 ?VA;O 26820==O=C G5@57 9>3> 740B=VABL 7<5=HC20B8 5D5:B8 >AB0==L>3>.

!;V4 7 >15@56=VABN >4=>G0A=> 70AB>A>2C20B8 =0?@>:A5= V7 :>@B8:>AB5@>W40<8 G5@57 ?V428I5=89 @878: 28=8=:5==O 28@07>: B0 :@>2>B5G C H;C=:>2>-.8H:>2>

0?@>:A5= =0B@VN <>65 7=878B8 03@530FVN B@><1>F8BV2 B0 ?@>4>268B8 G0A :@>2>B5GV, F5
A;V4 2@0E>2C20B8 ?@8 287=0G5==V G0AC :@>2>B5GV B0 ?@>BO3× AC?CB=L>3> ;V:C20==O
0=B8:>03C;O=B0<8.

5 @5:><5=4CTBLAO AC?CB=V9 ?@89× =0?@>A8=C, G5@57 2W @5G>28=8, 0 A0<5 =0?@>:A5=C.
0=V 4>A;V465=L =04 B20@8=0<8 ?>:07CNBL <>6;82VABL 28=8:=5==O AC4×, A?@8G8=5=8E
EV=>;>=>28<8 0=B81V>B8:0<8. 0FVT=B8, I> ?@89<0NBL EV=>;>=8, <0NBL ?V428I5=89 @878:
@>728B:C AC4>

A:V;L:8 =0?@>:A5= <0965 ?>2=VABN 7207CTBLAO 7 1V;:0<8 ?;07<8, 9>3> A;V4 7 >15@56=VABN
70AB>A>2C20B8 ?@8 AC?CB=L>EV4=8<8 3V40=B>W=C B0 ?>EV4=8<8 AC;LD0=V;A5G>28=8.

0?@>:A5= <>65 7<5=HC20B8 =0B@V9C@5B8G=C 4VN DC@>A5

0?@>:A5= <>65 7<5=HC20B8 0=B83V?5@B5=782=C 4VN 70A>1V2 ?@>B8 3V?5@B>=VW.

@8 AC?CB=L>:A5=C =0B@VN :=F5=B@0FVO ;VBVN 2 ?;072V 71V;LHCTBLAO.

0?@>:A5=, O: V ;V:0@AL:V 70A>18 3@C?8 , <>65 7<5=HC20B8 0=B83V?5@B5=782=C 4VN

?@>?@0=>;>;C B0 V=H8E 15B0-1;>:0B>@V2 B0 <>65 71V;LHC20B8 @878: =8@:>2>W

=54>AB0B=>ABV C ?0FVT=BV2, O:V ?0@0;5;L=> ?@89<0NBL V=3V1VB>@8 \$.

0?@>:A5= 7<5=HCT :0=0;LF52C A5:@5FVN <5B>B@5:A0BC, B>3> ?@89>:A8G=VABL<5B>B@5:A0BC
<>65 71V;LH8B8AL.

@8 AC?CB=L>15=5F84C ?@>4>26CTBLAO 1V>;>3VG=89 ?5@V>4 =0?V2282545==O =0?@>:A5=C B0
71V;LHCNBLAO 9>3> :=F5=B@0FVW 2 ?;07

!C?CB=V9 ?@89>< F8;:>A?>@8=C <>65 71V;LH8B8 @878: ?>@CH5==O DC=:FVW =8@>:.

>A;V465==O *Vn vitro* ?>:070;8, I> ?@8 AC?CB=L>:A5=C =0B@VN B0 784>2C48=C 71V;LHCNBLAO

:>=F5=B@0FVW >AB0==L>3> 2 ?;07

"5@ABV.

5 @>:V2.

#<>28 715@V30==O.

;O ;V:0@AL:>3> ?@5?0@0BC =5 ?>B@V1=V A?5FV0;L=V C<>28 715@V30==O. "@8<0B8 1;VAB5@ 2
7>2=VH=V9 C?0:>2FV 4;O 70E8ABC 2V4 4VW A2VB;0. 15@V30B8 2 =54>ABC?=>

#?0:>2:0.

10 B01;5B>:, 2:@8B8E ?;V2:>2>N >1>;>=:>N, C 1;VAB5@V, ?> 1 01> ?> 2 1;VAB5@8 C :0@B>==V9
:>@>1FV.

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

57 @5F5?B0.