

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

"\$
(ORTOPHEN)

!,:04:
4VNG0 @5G>28=0: 48;,>D5=0: =0B@VN;
1 B01;5B:0 D5=0:C =0B@VN 25 <3;
4>?>28=8: ;0:B>78 <=>3V4@0B, FC:>@ 1V;89, :@>E<0;L :0@B>?;O=89, ?>2V4>= 25, <03=VN
AB50@0B, <5B0:@8;0B=>3> A>?>;V<5@C 48A?5@AVO, ?@>?V;5=3;V:>;L, B0;L:, B8B0=C 4V>:A84
(171), 6>2B89 70EV4 FCF (E 110).

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV >1>;>=:>N, :8H:>2>@>7G8==V.
A=>2=V DV78:>-EVABV: B01;5B:8, 2:@8BV >1>;>=:>N 2V4 6>2B>3> 4> >@0=652>3> :>;L>@C, 7
42>>?C:>;>N ?>25@E=5N. 0 @>7;073;O40==V 70 4>?><>3>N ;C?8 284=> O4@>, >B>G5=5 >4=8<
ACFV;L=8< H0@>

\$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 >FB>2>W :8A;>B8 V A?>@V4=5=V A?>;C:8.>4 "% 0105.

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

\$0@<0:>48=0
8;,>D5=0: T =5AB5@>W4=8< ?@>B870?0;L=8< 70A>1>< () 7 28@065=8<8 7=51>;N20;L=8<,
?@>B870?0;L=8< B0 60@>7=86C20;L=8< 5D5:B0<8. A=>2=89 <5E0=V7< 4VW V=3V1C20==O
1V>A8=B57C ?@>AB03;0=48=V2, O:V 2V4V3@0NBL >A=>2=C @>;L C 28=8:=5==V 70?0;5==O, 1>;N
B0 30@OG:8.

In vitro, ?@8 :>=F5=B@0FVOE, 5:2V20;5=B=8E :>=F5=B@0FVO<, O:V 4>AO30NBLAO C ;N48=8,
48;,>D5=0: =5 ?@83=VGCT 1V>A8=B57 ?@>B5>3;V:0=C C E@OI>2V9 B:0=8=V.
"01;5B:8 @B>D5=C 7024O:8 H284:>;N V 70?0;5==V 48;,>D5=0: H284:> ?>;53HCT O: A?>=B0==89 1V;L,
B0: V 1V;L ?@8 @CE0E, 0 B0:>6 7<5=HCT =01@O;;VABL ?@8 70?0;5==V B0 =01@O: C 4V;O=FV @0=8.
@V< B>3>, 48;,>D5=0: <>65 ?>A;01;N20B8 1V;L V 7<5=HC20B8 :@>2>B5GC ?@8 ?5@28==V9 48A
<5=>@5W. 8;,>D5=0: B0:>6 7C<>2;NT 7=51>;N20;L=C 4VN ?@8 V=H8E AB0=0E, I>
AC?@>2>46CNBLAO ?> 28@065=8< V A8;L=8< 1>;5

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

1A>@1FVO.

8;,>D5=0: H284:> V ?>2=VABN 01A>@1CTBLAO. A<:BC20==O ?>G8=0TBLAO 157?>A5@54=L> ?VA;O
70AB>AC20==O ?@5?0@0BC, 0 :V;L:VABL 01A>@1>20=>W @5G>28=8 2V4?>2V40T :V;L:>ABV, I>
01A>@1CTBLAO ?@8 ?@89>W 4>78 48;,>D5=0:C =0B@VN, I> 70AB>A>2CTBLAO C 283;O4V
30AB@>@578AB5=B=8E B01;5B>:. @8 70AB>AC20==V ?@5?0@0BC ?V4 G0A 26820==O W6V =5
2V41C20TBLAO 2?;82C =0 :V;L:VABL 01A>@1>20=>3> 48;,>D5=0:C, E>G0 ?>G0B>: V H284:VABL 2A
<>:BC20==O <>6CBL 45I> C?>2V;L=N20B8AO.
>7?>4V;.

8;,>D5=0: =0 99,7 % 7207CTBLAO 7 1V;;0<8 A8@>20B:8 :@>2V, 3>;>2=8< G8=>< 7 0;L1C< (99,4 %). 1T
< @>7?>4V;C AB0=>28BL 0,12-0,17 ;/:3.

8;,>D5=0: ?@>=8:0T C A8=>2V0;L=C @V48=C, 45 9>3> <0:A8<0;L=V :>=F5=B@0FVW 4>AO30NBLAO
G5@57 2-4 3>48=8 ?VA;O 4>AO3=5==O <0:A8<0;L=8E 7=0G5=L C ?;072V. #O2=89 ?5@V>4
=0?V2282545==O V7 A8=>2V0;L=>W @V48=8 AB0=>28BL 3-6 3>48=. '5@57 2 3>48=8 ?VA;O
4>AO3=5==O <0:A8<0;L=8E @V2=V2 C ?;072V :>=F5=B@0FVW 4VNG>W @5G>28=8 C A8=>2V0;L=V9
@V48=V T 28I8<8, =V6 C ?;072V, V 70;8H0NBLAO B0:8<8 I5 ?@>BO3>< 12 3>48=.

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

V>B@0=AD>@<0FVO 48;,>D5=0:C G0AB:>2> 2V41C20TBLAO H;OE>< 3;N:C@>=V70FVW V=B0:B=>W
<>;5:C;8, 0;5 3>;>2=8< G8=>< H;OE>< >4=>@07>2>3> V 1030B>@07>2>3> 3V4@>:A8;N20==O B0
<5B>:A8;N20==O.

82545==O.

>2=89 A8AB5<=89 ;V@5=A 48;:>D5=0:C 7 ?;07<8 :@>2V AB0=>28BL 263±56 <;/E2 (A5@54=T ± AB0=40@B=5 2V4E8;5==O). V=F5289 ?5@V>4 =0?V2282545==O AB0=>28BL 1-2 3>48=8. 5@V>4 =0?V2282545==O 4-E <5B01>;VBV2, 2;NG0NG8 2 0:B82=8E, AB0=>28BL 1-3 3>48=8. \$0:B8G=> =50:B82=89 <5B01>;VB <0T =01030B> 4>2H89 ?5@V>4 =0?V2282545==O.
@81;87=> 60 % 4>78 282>48BLAO V7 A5G5N C 283;O4V <5B01>;VBV2, 0 <5=H5 1 % C 283;O4V =57W @5G>28=8. 5HB0 4>78 282>48BLAO C 283;O4V <5B01>;VBV2 7 6>2GN B0 :0;:>
\$0@<0>.:V=5B8:0 2 >.:@5<8E 3@C?0E ?0FVT=BV2.
5 A?>AB5@V30;>AO ACBBT28E 2V4AB59 2A<.:BC20==O, <5B01>;V7 2V4 2V:C ?0FVT=B0.
?0FVT=BV2 7 ?>@CH5==O<8 DC=:FVW =8@>.:V=5B8:0 @07>2>W 4>78 ?@5?0@0BC =5 2:07CT =0 VA=C20==O 1C4L-O:>W D>@<8 :CW 4VNG>W @5G>28=8 ?@8 728G09=V9 AE5AC20==O ?@5?0@0BC.
?0FVT=BV2 7 ;V@5=A<.:@50B8=V=C <5=H5 10 <;/E2 B5>@5B8G=V @V2=>206=V :>=F5=B@0FVW <5B01>;VBV2 C ?;072V ?@81;87=> C 4 @078 28IV, =V6 C 74>@>28E 4>1@>2>;LFV2. @>B5 2 :V=F52>

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

>:070==O.

- 0?0;L=V V 4535=5@0B82=V D>@<8 @52<0B8G=8E 70E2>@N20=L (@52<0B>W4=89 0@B@8B, 0=:V;>7CNG89 A?>=48;VB, >AB5>0@B@>7, A?>=48;>0@B@8B8), 1>;L>2V A8=4@>8 7 ;>:0;V70FVTN C E@51BV, =5AC3;>1>289 @52<0B87<;
- 3>AB@V =0?048 ?>403@8;
- ?>ABB@02<0B8G=V V ?VA;O>?5@0FV9=V 1>;L>2V A8=4@>8, I> AC?@>2>46CNBLAO 70?0;5==O < V =01@O:0<8, =0?@8;:04 ?VA;O AB<0B>;>3VG=8E V >@B>?548G=8E 2B@CG0=L;
- 3V=5>;>3VG=V 70E2>@N20==O, I> AC?@>2>46CNBLAO 1>;L>28< A8=4@><< V 70?0;5==O<, =0?@8;:04 ?5@28==0 48A<5=>@5O 01> 04=5:A8B;
- O: 4>?>@N20==OE ->@30=V2, I> AC?@>2>46CNBLAO 2V4GCBBO< 1>;N, =0?@8;:04 ?@8 D0@8=3>B>=78;VBV, >B8BV.
>B@8A=>2=5 70E2>@N20==O A;V4 ;V:C20B8 70A>10<8 1078A=>W B5@0?VW. 0@OG:0 A0<0 ?> A>1V =5 T ?>:070==O< 4;O 70AB>AC20==O ?@5?0@0BC.

@>B8?>:070==O.

- V?5@GCB;82VABL 4> 4VNG>W @5G>28=8 01> 4> 1C4L-O:8E V=H8E :>5=BV2 ?@5?0@0BC.
- ;5@3VG=V @50:FVW 2 0=0<=57V C 283;O4V 1@>=E>A?07?82O=:8, 3>AB@>3> @8=VBC, =070;L=8E ?>;V?V2 01> A8<8, ?>4V1=V 4> 0;5@3VW, ?VA;O 70AB>AC20==O 0F5B8;A0;VF8;>2>W :8A;>B8 01> V=H8E =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2.
- 8@07:0 H;C=:0 B0/01> 4C>45=0;L=V 28@07:8, H;C=:>2>:8H:>2V :@>2>B5GV 01> ?5@D>@0FVO.
- 0?0;L=V 70E2>@N20==O :8H5G=8:0 (E2>@>10 @>=0 01> 28@07:>289 :>;VB).
- "O6:0 ?5GV=:>20 =54>AB0B=VABL (;0A ! 70 H:0;>N '09;4- N, F8@>7 ?5GV=:8 B0 0AF8B).
- "O6:0 =8@:>20 =54>AB0B=VABL (;V@5=A :@50B8=V=C<30 <;/E2).
- 0ABV9=0 A5@F520 =54>AB0B=VABL (NYHA II-IV).
- □H5@>10 A5@FO C ?0FVT=BV2, O:V <0NBL AB5=>:0@4VN, ?5@5=5A5=89 V=D0@:B:0@40.
- ?O@=V 70E2>@N20==O C ?0FVT=BV2, O:V ?5@5=5A;8 V=AC;LB 01> <0NBL 5?V7>48 B@0=78B>@=8E VH5
- 0E2>@N20==O ?5@8D5@8G=8E 0@B5@V9.
- V:C20==O ?5@V>?5@0FV9=>3> 1>;N ?@8 0>@B>:>@>=0@=> 28:>@8AB0==O 0?0@0BC HBCG=>3> :@>2>>1V3C).

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

@8 70AB>AC20==V @V7=8E 4>7 B0 D>@< 48;:>D5=0:C A?>AB5@V30;8AO =0ABC?=V 2848 270T <>4VW.

VBV9. @8 >4=>G0A=>AC20==V 48;:>D5=0: <>65 ?V428IC20B8 :>=F5=B@0FVW ;VBVN C ?;072V. 5:> <5=4>20=> ?@>2>48B8 :>=B@>;L @V2=O ;VBVN C A8@>20BFV :@>2V.

83>:A8=. @8 >4=>G0A=>AC20==V 48;:>D5=0: <>65 ?V428IC20B8 :>=F5=B@0FVW 483>:A8=C C ?;07 2V. 5:>5=4>20=> ?@>2>48B8 :>=B@>;L @V2=O 483>:A8=C C A8@>20BFV :@>2V.

!5G>3V==V V 0=B83V?5@B5=782=V 70A>18. /: V 7 V=H8<8 , >4=>G0A=5 70AB>AC20==O 48;:>D5=0:C B0 A5G>3V==8E 01> 0=B83V?5@B5=782=8E ?@5?0@0BV2 (=0?@8;:04, 15B0-04@5=>1>;:0B>@V2,

V=3V1VB>@V2 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC (\$)) <>65 ?@872>48B8 4> 7=865==O
0=B83V?5@B5=782=>3> 5D5:BC. "><1V=0FVN F8E ?@5?0@0BV2 A;V4 70AB>A>2C20B8 7
>15@56=VABN; 0 ?0FVT=B0<, >A>1;82> ;VB=L>3> 2V:C, A;V4 ?5@V>48G=> :>=B@>;N20B8
0@B5@V0;L=89 B8A:. 0FVT=B8 ?>28==V >B@878 @V48=8, 0 B0:>6 A;V4 ?@>2>48B8 :>=B@>;L
DC=:FVW =8@>: ?VA;O ?>G0B:C :<1V=>20=>W B5@0?VW, 0 =040;V @53C;O@=>, >A>1;82> ?@8
70AB>AC20==V 4VC@5B8:V2 B0 V=3V1VB>@V2 \$ C 72O7:C 7 ?V428I5=8< @878:><
=5D@>B>:A8G=>ABV. 4=>G0A=5 ;V:C20==O V7 70AB>AC20==O< :0;V9715@V30NG8E 4VC@5B8:V2
<>65 A?@8G8=8B8 ?V428I5==O @V2=O :0;VN C A8@>20BFV :@>2V, B>ABV9=> ?5@52V@OB8.
=HV V :>@B8:>AB5@>W48. 4=>G0A=5 70AB>AC20==O 48;>D5=0:C 7 V=H8<8 A8AB5<=>W 4VW 01>
:>@B8:>AB5@>W40<8 <>65 71V;LHC20B8 G0AB>BC 28=8:=5==O ?>1VG=8E @50:FV9 7 1>:C
H;C=:>2>-.8H:>2>3> B@0:BC (").
=B8:>03C;O=B8 V 0=B8B@><1>B8G=V 70A>18 ?@87=0G0NBL 7 >15@56=VABN, >A:V;L:8
>4=>G0A=5 70AB>AC20==O 7 48;>D5=0:>< <>65 ?V428IC20B8 @878: 28=8:=5==O :@>2>B5GV. :>@5
2V4><;5==O ?@> ?V428I5=89 @878: 28=8:=5==O :@>2>B5GV C ?0FVT=BV2, O:V >4=>G0A=>
70AB>A>2CNBL 48;>D5=0: V 0:B8:>03C;O=B8. 5:<5=4>20=89 ?>ABV9=89 :>=B@>;L AB0=C B0:8E
?0FVT=BV2.
!5;5:B82=V V=3V1VB>@8 72>@>B=>3> 70E>?;5==O A5@>B>=V=C (!). 4=>G0A=5 ?@87=0G5==O
A8AB5<=>W 4VW, 2;;NG0NG8 48;>D5=0:, B0 !! <>65 ?V428IC20B8 @878: 28=8:=5==O :@>2>B5GV C (".
=B84V015B8G=V ?@5?0@0B8. 8;>D5=0: <>6=0 ?@87=0G0B8 >4=>G0A=> 7 ?5@>@0;L=8<8
0=B84V015B8G=8<8 ?@5?0@0B0<8 157 2?;82C =0 WE ;V=VG=89 5D5:B. @>B5 1C;8 >:@52V4><;5==O
?@> 3V?5@3;V:53;V:5 ?>B@51CT :>@83C20==O 4>78 0=B84V015B8G=8E ?@5?0@0BV2. 5:>
<5=4>20=89 :>=B@>;L @V2=O 3;N:>78 2 :@>2V ?@>BO3< :<1V=>20=>W B5@0?VW.
5B>B@5:A0B. >15@56=VABN 70AB>A>2CNBL =5<5=H5 =V6 70 24 3>48=8 ?5@54 01> ?VA;O
;V:C20==O <5B>B@5:A0B><, >A:V;L:8 :>=F5=B@0FVW <5B>B@5:A0BC C :@>2V <>6CBL 7@>AB0B8
V ?>A8;N20B8 B>:A8G=VABL.
?>A?>@8=. 8;>D5=0:, O: V V=HV , <>65 ?V428IC20B8 =5D@>B>:A8G=VABL F8;>A?>@8=C
2=0A;V4>: 2?;82C =0 =8@>:2V ?@>AB03;0=48=8. ">D5=0: A;V4 70AB>A>2C20B8 C 4>70E =86G8E, =V6
4;O ?0FVT=BV2, O:V =5 70AB>A>2CNBL F8;>A?>@8=.
=B81V>B8:8 EV=>;>=>2>3> @O4C. C;8 >:@52V4><;5==O ?@> AC4><8, 28=8:=5==O O:8E <>3> 1CB8
?>2O70=5 7 >4=>G0A=8< 70AB>AC20==O< EV=>;>=V2 B0 .
>BC6=V V=3V1VB>@8 CYP2C9. >15@56=VABN >4=>G0A=> ?@87=0G0NBL 48;>D5=0: B0
V=3V1VB>@8 CYP2C9 (B0:8E O: AC;LDV=V;?V@07>= V 2>@8:>=07>;), B0: O: F5<>65 ?@8725AB8 4>
7=0G=>3> 71V;LH5==O<0:A8<0;L=>W :>=F5=B@0FVW 2 ?;07D5=0:C, C 72O7:C 7 V=3V1C20==O< 9>3>
<5B01>;V7
\$5=VB>W=. @8 70AB>AC20==V D5=VB>W=C >4=>G0A=> 7 48;>D5=0:>< @5:><5=4>20=>
74V9A=N20B8 <=>VB>@8=3 :>=F5=B@0FVW 2 ?;07W=C C 72O7:C 7 <>6;828< 71V;LH5==O< 2?;82C
D5=VB>W=C.

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

V4?>2V4=> 4> 7030;L=?>@89=OB8E ?V4E>4V2 4> ;V:C20==O V=D5:FV9=>-70?0;L=8E 70E2>@N20=L
=5>1EV4=> B0:>6 70AB>A>2C20B8 5BV>B@>?>=V 70A>18. 7>;L>20=5 ?V428I5==O B5:070==O< 4;O
70AB>AC20==O ?@5?0@0BC.

/: V V=HV , @B>D5= 7024O:8 A2>W< D0@<0:>48=0

030;L=V 70AB5@565==O I>4> 70AB>AC20==O A8AB5<=>W 4VW.

;O 7<5=H5==O @878:C 28=8:=5==O 30AB@>V=B5AB8=0;L=>W 28@07:8, :@>2>B5GV 01>

?5@D>@0FVW, I> <>6CBL 28=8:0B8 C 1C4L-O:89 ?5@V>4 ;V:C20==O , =570;56=> 2V4 WE

A5;5:B82=>ABV I>4> &-2 V =02VBL ?@8 2V4ACB=>ABV A8D0:B>@V2 AE8;L=>ABV 2 0=0<=57V,

A;V4 70AB>A>2C20B8 =09<5=HV 5D5:B82=V 4>78 ?@>BO3< =09:>@>BH>3> ?5@V>4C G0AC.

0FVT=B0< 7 ?>@CH5==O<8 7 1>:C H;C=:>2>-.8H:>2>3> B@0:BC, ?>@CH5==O<8 DC=:FVW ?5GV=:8

01> 7 ?V4>7@>N =0 28@07:C H;C=:0 01> :8H5G=8:C 2 0=0<=57V 40=89 ?@5?0@0B A;V4

70AB>A>2C20B8 ;8H5 C 28?04:C 01A>;NB=>3> ?>:070==O V ?V4 @5B5;L=8< <548G=8< =03;O4>

V47=0G02AO ?V428I5=89 @878: 28=8:=5==O B@><1>B8G=8E V F5@51@>20A:C;O@=8E CA:;04=5=L

?@8 70AB>AC20==V ?52=8E A5;5:B82=8E V=3V1VB>@V2 &-2. 0 40=89 G0A B>G=> =52V4><>, G8

B0:89 @878: :>@5;NT 157?>A5@54=L> 7 &-1/&-2 A5;5:B82=VABN >:@58E .

A:V;L:8 =0 40=89 G0A 4;O ?>@V2=O==O =5<0T 40=8E I>4> B@820;>3> ;V:C20==O 48;>D5=0:>< C

<0:A8<0;L=8E 4>70E, =5 <>6=0 28;;NG8B8 VA=C20==O ?>4V1=>3> ?V428I5=>3> @878:C. > B>3>
G0AC, ?>:8 =5 1C4CBL >B@8<0=V B0:V 40=V, A;V4 @5B5;L=> >FV=N20B8 A?V22V4=>H5==O @878:-
:>@8ABL ?5@54 ?@87=0G5==O< 48;;>D5=0:C ?0FVT=B0< 7 ;;V=VG=> ?V4B25@465=>N VH5N
E2>@>1>N A5@FO, F5@51@>20A:C;O@=8<8 @>7;040<8, >1;VB5@CNG8<8 70E2>@N20==O<8
?5@8D5@8G=8E 0@B5@V9.
@87=0G0B8 48;;>D5=0: ?0FVT=B0< V7 7=0G=8<8 D0:B>@0<8 @878:C :0@4V>20A:C;O@=8E O28I
(=0?@8;;04 3V?5@B>=VO, 3V?5@;V?V45289 4V015B, ?0;V==O) <>6=0 ;8H5 ?VA;O @5B5;L=>W
;;V=VG=>W >FV=:8. A:V;L:8 :0@4V>20A:C;O@=V @878:8<>6CBL 7@>AB0B8 V7 71V;LH5==O< 4>78
B0 B@820;>ABV ;V:C20==O, 9>3> =5>1EV4=> 70AB>A>2C20B8 O:>>30 :>@>BH89 ?5@V>4 B0 C
=09=86GV9 5D5:B82=V9 4>7V. !;V4 ?5@V>48G=> ?5@53;O40B8 ?>B@518 ?0FVT=B0 C 70AB>AC20==V
48;;>D5=0:C 4;O ?>;53H5==O A82V4L =0 B5@0?VN.
>15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< AB0@H5 65 @>:V2.
?;82 =0 =8@:8 7C<>2;NT 70B@8 0@B5@V0;L=C 3V?5@B5=7VN. ">D5=0: A;V4 70AB>A>2C20B8 7
>15@56=VABN ?0FVT=B0< 7 ?>@CH5==O< 7 1>:C A5@FO 01> V=H8<8 AB0=0<8, ?@8 O:8E T
AE8;L=VABL 4> 70B@8I5@56=VABN 70AB>A>2CNBL ?@5?0@0B ?0FVT=B0<, O:V >4=>G0A=>
70AB>A>2CNBL 4VC@5B8:8 01> V=3V1VB>@8 \$, 01> <0NBL ?V428I5=89 @878: @>728B:C 3V?>2>;5
;O 2AVE E0@0:B5@=V H;C=:>2>:-8H:>2V :@>2>B5GV, 28@07:8 B0 ?5@D>@0FVW, O:V<>6CBL 1CB8
;5B0;L=8<8, B0 <>6CBL 28=8:0B8 C ?5@V>4 ;V:C20==O =0 B;V ?@>4@<0;L=8E A8 C @07V WE
2V4ACB=>ABV, 01> C ?0FVT=BV2 V7 A5@9>7=8<8 H;C=:>2>:-8H:>28<8 O28I0<8 2 0=0<=57V. 030;>
B0:V O28I0 =091V;LH =5157?5G=V 4;O ?0FVT=BV2 ;VB=L>3> 2V:C. >:@5<8E 28?04:0E, :>;8 C
?0FVT=BV2, O:V 70AB>A>2CNBL @B>D5=, @>72820NBLAO FV CA;;04=5==O, ?@5?0@0B A;V4 2V4
C65 @V4:> C 7207:C V7 70AB>AC20==O<, 2;;NG0NG8 @B>D5=, ?>2V4><;O;>AO ?@> A5@9>7=V
@50:FVW 7 1>:C H:V@8 (C 45O:8E 28?04:0E ;5B0;L=V), 2;;NG0NG8 5:AD>;V0B82=89 45@<0B8B,
A8=4@<< !BV25=A0-6>=A>=0 V B>:A8G=89 5?V45@<0;L=89 =5:@>;V7. 0928I89 @878: 28=8:=5==O
B0:8E @50:FV9 C ?0FVT=BV2 VA=CT =0 ?>G0B:C ;V:C20==O, O: ?@028;>, 2V41C20TBLAO C?@>4>26
1-3> D5= A;V4 2V4O2V ?5@H8E >7=0: 28A8?0=L, C@065==OE A;87>28E >1>;>=: 01> 1C4L-O:8E
V=H8E >7=0: 3V?5@GCB;82>ABV.
/: V ?@8 70AB>AC20==V 2AVE 0=0;35B8:V2, ?@8 B@820;>AC20==V ?@5?0@0BC 4;O ;V:C20==O
3>;>2>=>3> 1>;N <>65 A?>AB5@V30B8AO ?>:@0I5==O 01> ?>3V@H5==O AB0=C (3>;>2=89 1V;L
G5@57 =04AC20==O ;V:0@AL:8E 70A>1V2). /:I> 3>;>2=89 1V;L 28=8:0T 2=0A;V4>: =04B>
70AB>AC20==O 0=0;35B8:V2, =5 A;V4 71V;LHC20B8 4>7C 0=0;35B8:V2, C B0:8E 28?04:0E ;V:C20==O
A;V4 ?@8?8=8B8. >;>2=89 1V;L 2=0A;V4>: =043> 70AB>AC20==O ?@5?0@0BV2 A;V4 70?V4>7@8B8 C
?0FVT=BV2 7 G0AB8<8 01> I>45==8<8 =0?040<8 3>;>2=>3> 1>;N, I> 28=8:0NBL, =572060NG8 =0
@53C;O@=5 70AB>AC20==O 0=0;L35B8:V2.
/: V ?@8 70AB>AC20==V V=H8E , @V4:> <>6CBL @>72820B8AO 0;5@3VG=V @50:FVW (2;;NG0NG8
0=0DV;0:B8G=V/0=0DV;0:B>W4=V @50:FVW), =02VBL 157 ?>?5@54=L>3> 70AB>AC20==O
48;;>D5=0:C.
\$5@B8;L=VABL.
/: V V=HV , @B>D5= <>65 2?;820B8 =0 6V=>GC D5@B8;L=VABL V B<5=4>20=89 6V=:0<, O:V
?;0=CNBL 203VB=VABL. !;V4 ?@8?8=8B8 70AB>AC20==O 40=>3> ?@5?0@0BC 6V=:0<, O:V =5
<>6CBL 70203VB=VB8, 0 B0:>6 6V=:0<, O:8< ?@>2>48BLAO >1AB565==O I>4> 157?;V44O.
0AB5@565==O.
030;L=V. !;V4 C=8:0B8 >4=>G0A=>3> 70AB>AC20==O ?@5?0@0BC @B>D5= B0 V=H8E A8AB5<=>W
4VW, 2;;NG0NG8 A5;5:B82=V V=3V1VB>@8 &-2, >A:V;L:8 =5<0T ?V4B25@465=L I>4> ?5@5203
A8=5@3VG=>W 4VW, 0 B0:>6 G5@57 28=8:=5==O 4>40B:>28E ?>1VG=8E 5D5:BV2.
!;V4 7>15@56=VABN 70AB>A>2C20B8 ?@5?0@0B ?0FVT=B0< ;VB=L>3> 2V:C. >:@5<0, @5:>
<5=4>20=> ?@87=0G0B8 =09=86GV 5D5:B82=V 4>78 DV78G=> A;01:8< ?0FVT=B0< ;VB=L>3> 2V:C 01>
O:I> <0A0 BV;0 ?0FVT=B0 =86G0 70 =>@
"01;5B:8 @B>D5= 7C, B>
@5?0@0B @, I> A;V4 2@0E>2C20B8 E2>@8< =0 FC:@>289 4V015B.
@>=EV0;L=0 0AB<0 2 0=0<=57V.
?0FVT=BV2, E2>@8E =0 1@>=EV0;L=C 0AB==8< 0;5@3VG=8< @8=VB><, =01@O:>< A;87>2>W
>1>;>=:8 =>A0 (=0?@8;;04 =070;L=V ?>;V?8), E@>=VG=8<8 >1AB@C:B82=8<8 70E2>@N20==O<8
;535=L (%) G8 E@>=VG=8<8 V=D5:FVO<8 48E0;L=>W A8AB5<8 (>A>1;82> 7 ?@>O20<8, ?>4V1=8<8 4>
A83> @8=VBC) ?@8 ?@89>1VG=V 5D5:B8, O: 703>AB@5==O 1@>=EV0;L=>W 0AB<8 (B0: 720=0

=5?5@5=>A8 0=0;35B8G=0 0AB<0), =01@O: 2V=:5, :@>?82O=:0. # 72O7:C 7 F8< B0:8< E2>@8<
=5>1EV4=V A?5FV0;L=V 70AB5@56=V 70E>48 (3>B>2=VABL 4> =040==O =52V4;:04=>W 4>?<>38).
8I5707=0G5=5 B0:>6 AB>ACTBLAO ?0FVT=BV2 7 0;5@3VG=8<8 ?@>O20<8 ?@8 70AB>AC20==V
V=H8E ?@5?0@0BV2, =0?@8;:04 28A8?0==O, A25@1V6, :@>?82O=:0.
?:82 =0 H;C=:>2>-.8H:>289 B@0:B (").
/: V ?@8 70AB>AC20==V V=H8E , @5B5;L=89 <548G=89 =03;O4 V >A>1;820 >15@56=VABL T
=5>1EV4=8<8 ?@8 ?@87=0G5==V ?@5?0@0BC @B>D5= ?0FVT=B0< V7 A8<0<8, I> 2:07CNBL =0
?>@CH5==O 7 1>:C H;C=:>2>-.8H:>2>3> B@0:BC, G8 7 2:07V2:>N =0 28@07:C, :@>2>B5GC 01>
?5@D>@0FVN H;C=:0 01> :8H5G=8:C 2 0=0<=57V. 878: 28=8=:5==O :@>2>B5GV (" ?V428ICTBLAO ?@8
71V;LH5==V 4>78 , 0 B0:>6 C ?0FVT=BV2 7 28@07:>N 2 0=0<=57V, >A>1;82> O:I> 1C;8 CA;:04=5==O
(:@>2>B5G0 01> ?5@D>@0FVO), B0 C ?0FVT=BV2 ;VB=L>3> 2V:C. ;O 7<5=H5==O @878:C
B>:A8G=>3> 2?;82C =0 (" C B0:8E ?0FVT=BV2 ;V:C20==O A;V4 @>7?>G8=0B8 B0 ?V4B@870E. ;O B0:8E
?0FVT=BV2, 0 B0:>6 4;O ?0FVT=BV2, O:8< =5>1EV4=5 >4=>G0A=5 70AB>AC20==O ?@5?0@0BV2, I>
2C :8A;>BC, G8 V=H8E ?@5?0@0BV2, I> ?V428ICNBL @878: =530B82=>3> 2?;82C =0 (" , A;V4
@>73;O=CB8 <>6;82VABL ?@87=0G5==O :<1V=>20=>W B5@0?VW V7 70AB>AC20==O< 70E8A=8E
70A>1V2 (=0?@8;:04, V=3V1VB>@V2 ?@>B>==>W ?> ?@>AB>;C). 0FVT=B8 7 B>:A8G=8< 2?;82< =0
(" 2 0=0<=57V, >A>1;82> ;VB=L>3> 2V:C, <0NBL ?>2V4<<8B8 ;V:0@O ?@> 1C4L-O:V =5728G=V 014>
?:82 =0 ?5GV=:C.
0FVT=B0< 7 ?>@CH5==O< 7 1>:C ?5GV=:8 A;V4 70157?5G8B8 ?>ABV9=89 <548G=89 =03;O4, >A:V;L:8
WE AB0= <>65 ?>3V@H8B8AO.
/: V ?@8 70AB>AC20==V V=H8E , <>6CBL 7@>AB0B8 @V2=V >4=>3> V 1V;LH5 D5@<5=BV2 ?5GV=:8.
&5 A?>AB5@V30;>AO 4C65 G0AB> ?@8 70AB>AC20==V 48;:>D5=0:C, 0;5 4C65 @V4:>
AC?@>2>46C20;>AO ?>O2>N ;;V=VG=8E A8ABV 28?04:V2 A?>AB5@V30;>AO 7@>AB0==O 4>
3@0=8G=8E @V2=V2.
@>AB0==O @V2=V2 ?5GV=:>28E D5@<5=BV2 AC?@>2>46C20;>AO ;;V=VG=8<8 ?@>O20<8
C@065==O ?5GV=:8.
@>AB0==O @V2=V2 D5@<5=BV2 1C;>, O: ?@028;>, >1>@>B=8< ?VA;O ?@8?8=5==O 70AB>AC20==O
?@5?0@0BC.
!;V4 707=0G8B8, I> ?@5?0@0B @B>D5= @5:<5=4>20=89 ;8H5 4;O :>@>B:>3> :C@AC ;V:C20==O (=5
1V;LH5 2 B86=V2). # 28?04:C ?@87=0G5==O 48;:>D5=0:C =0 B@820;89 ?5@V>4 70AB5@56=8< 70E>4><
T @53C;O@=5 A?>AB5@565==O 70 DC=:FVTN ?5GV=:8. 0AB>AC20==O 40=>3> ?@5?0@0BC A;V4
?@8?8=8B8, O:I> A?>AB5@V30TBLAO ?>@CH5==O 01> ?>3V@H5==O DC=:FVW ?5GV=:8, O:I>
;;V=VG=V >7=0:8 01> A8<8 A2V4G0BL ?@> @>728B>: 70E2>@N20==O ?5GV=:8 01> O:I> 28=8:0NBL
V=HV A8<8, =0?@8;:04 5>78=>DV;VO, 28A8?0==O. 5?0B8B <>65 28=8:0B8 157 ?@>4@><0;L=8E A8
:@V< 7@>AB0==O @V2=V2 ?5GV=:>28E D5@<5=BV2, ?>2V4<<O;>AO ?@> BO6:V @50:FVW 7 1>:C
?5GV=:8, 2;:NG0NG8 6>2BO=8FN V DC;L7 ?5GV=:8 V ?5GV=:>2C =54>AB0B=VABL, I> C 45O:8E
28?04:0E 1C;8 ;5B0;L=8<8.
>15@56=VABN 70AB>A>2CNBL 48;:>D5=0: ?0FVT=B0< 7 ?5GV=:>2>N ?>@DV@VTN G5@57 9
<>2V@=VABL ?@>2>:C20==O =0?04C.
?:82 =0 =8@:8.
"@820;5 70AB>AC20==O 28A>:8E 4>7 G0AB> ?@872>48BL 4> 28=8=:5==O =01@O:V2 V
0@B5@V0;L=>W 3V?5@B5=7VW.
A>1;82>W >15@56=>ABV A;V4 4>B@870;:VB8==>W @V48=8, =0?@8;:04 ?5@54/?VA;O
EV@C@3VG=8E 2B@CG0=L. @8 ?@87=0G5==V C B0:8E 28?04:0E @B>D5=C ?@>2>4OBL
<=>VB>@8=3 DC=:FVW =8@>:. VA;O ?@8?8=5==O B5@0?VW AB0= ?0FVT=BV2 70728G09 =>@
<0;V7CTBLAO.
?:82 =0 35<0B>;>3VG=V ?>:07=8:8.
@5?0@0B @B>D5= @5:<5=4>20=89 ;8H5 4;O :>@>B:>G0A=>3> :C@AC ;V:C20==O. # @07V
?@87=0G5==O 40=>3> ?@5?0@0BC =0 B@820;VH89 ?5@V>4 @5:<5=4CTBLAO (O: V 4;O V=H8E)
@53C;O@=> :>=B@>;N20B8 35<>3@0
/: V V=HV , 48;:>D5=0: <>65 B82> V=3V1C20B8 03@530FVN B@<1>F8BV2, B> :>=B@>;N20B8 AB0=
?0FVT=BV2 7 ?>@CH5==O< 35<>AB07C.

0AB>AC20==O ?V4 G0A 203VB=>ABV B0 3>4C20==O 3@C44N.

03VB=VABL.>A;V465==O 70AB>AC20==O 48;:>D5=0:C 203VB=8< 6V=:0< =5 ?@>2>48;8AO. @5?0@0B
=5 A;V4 70AB>A>2C20B8 ?@>BO3<< I-II B@8<5AB@V2 203VB=>ABV, 70 28=OB:<, O:I> ?>B5=V9=0
:>@8ABL ?@89>

5@V>4 3>4C20==O 3@C44N. >4V1=> 4> V=H8E , 48;:>D5=0: C =525;8:8E :V;L:>ABOE ?@>=8:0T C
3@C4=5 <>:>:, B>4 3>4C20==O 3@C44N, I>1 C=8:=CB8 @>728B:C ?>1VG=8E 5D5:BV2 C 48B8=8.

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.

0728G09 ?@8 ?@89><5=4>20=V9 4>7V V ?@8 :>@>B:>G0A=>AB5@V30TBLAO. @>B5 ?0FVT=B0<, C
O:8E ?@8 70AB>AC20==V ?@5?0@0BC 28=8:0NBL ?>@CH5==O 7>@C, 70?0<>@>G5==O, 25@B8<>,
A>=;82VABL 01> V=HV ?>@CH5==O F5=B@0;L=>W =5@2>2>W A8AB5<8 (&!), =5 A;V4 :5@C20B8
02B>B@0=A?>@B<< 01> ?@0FN20B8 7 <5E0=V7<0<8.

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

0AB>AC20==O ?@5?0@0BC A;V4 @>7?>G8=0B8 O:<>30 @0=VH5 ?VA;O ?@>O2C ?5@H8E 1>;L>28E
A8 2V4 A8<0B8:8, AB0=>28BL 4> :V;L:>E 4V1.

@5?0@0B A;V4 70AB>A>2C20B8 C =09<5=H8E 5D5:B82=8E 4>70E ?@>BO3<< =09:>@>BH>3>
?5@V>4C G0AC, 2@0E>2CNG8 70240==O ;V:C20==O C :>6=>3> >:@5<>3> ?0FVT=B0.

;O 4>@>A;8E @5:><5=4>20=0 ?>G0B:>20 4>1>20 4>70 AB0=>28BL 100-150 <3. # ;53:8E 28?04:0E, O: V
?@8 4>23>AB@>:>2V9 B5@0?VW, 70728G09 4>AB0B=L> ?@87=0G5==O 75-100<3.

030;L=0 4>1>20 4>70 4;O 4>@>A;8E 70728G09 @>7?>4V;OTBLAO =0 2-3 ?@89><8. >1>20 4>70
?@5?0@0BC =5 <0T ?5@528IC20B8 150 <3.

@8 ?5@28==V9 48A<5=>@5W 4>1>2C 4>7C ?V418@0NBL V=482V4C0;L=>, V 70728G09 2>=0
AB0=>28BL 50-150 <3. >G0B:>20 4>70 <>65 AB0=>28B8 50-100 <3, 0;5 ?@8 =5>1EV4=>ABV WW
<>6=0 2?@>4>26 :V;L:>E <5=AB@C0;L=8E F8;:V2 ?V428I8B8, 0;5 =5 28I5 =V6 4> 200 <3/4>1C. VBO<
2V4 8 @>:V2 (7 <0A>N BV;0 =5 <5=H5 25 :3) 4> 14 @>:V2 70AB>A>2CNBL B01;5B:8 ?> 25 <3 70
?@87=0G5==O< ;V:0@O C 4>1>2V9 4>7V 1-2<3/:3 <0A8 BV;0 70;56=> 2V4 BO6:>ABV A87C
@>74V;ONBL =0 2-3 ?@89><8.

0?@8;:04, 4;O 48B8=8 7 <0A>N BV;0 30 :3 4>1>20 4>70 <>65 AB0=>28B8 2V4 30 4> 60 <3. 8E>4OG8 7
FL>3> 4V0?07>=C, 48B8=V <>6=0 ?@87=0G8B8 ?> 1 B01;5BFV ?> 25 <3 2 @078 =0 4>1C.

@8 ;V:C20==V N25=V;L=>3> @52<0B>W4=>3> 0@B@8BC 4>1>20 4>70 <>65 1CB8 ?V428I5=0 4> 3
<3/:3 <0:A8<0;L=>W 4>1>2>W 4>78. 5 A;V4 ?5@528IC20B8 <0:A8<0;L=C 4>1>2C 4>7C 150 <3.

VB8.

VBO< 2V4 8 @>:V2 (7 <0A>N BV;0 =5 <5=H5 25 :3) 4> 14 @>:V2 ?@5?0@0B ?@87=0G0B8 ;8H5 C
283;04V B01;5B>: ?> 25 <3. VBO< 2V4 14 @>:V2 <>6=0 ?@87=0G0B8 B01;5B:8 ?> 50 <3.

5@54>7C20==O.

!8<8. "8?>2>W ;:V=VG=>W :0@B8=8 ?@8 ?5@54>7C20==V 48;:>D5=:C =5<0T. @8 ?5@54>7C20==V
<>6CBL 28=8:0B8 B0:V A8<8: 1;N20==O, 30AB@>V=B5AB8=0;L=0 :@>2>B5G0, 4V0@5O, 70?0
<>@>G5==O, 472V= C 2CE0E 01> AC4<<8. # 28?04:C BO6:>3> >B@CT==O <>6;8289 @>728B>:
3>AB@>W =8@:>2>W =54>AB0B=>ABV B0 C@065==O ?5GV=:8.

V:C20==O. V:C20==O 3>AB@>3> >B@CT==O =5AB5@>W4=8<8 ?@>B870?0;L=8<8 70A>10<8 (),
2;:NG0NG8 48;:>D5=0:, 70728G09 ?>;O30T C ?@>2545==V ?V4B@84V2 V A8<0B8G=>3> ;V:C20==O
B0:8E CA;:04=5=L, O: 0@B5@V0;L=0 3V?>B5=7VO, =8@:>20 =54>AB0B=VABL, AC4<<8, ?>@CH5==O 7
1>:C H;C=:>2>:8H:>2>3> B@0:BC, ?@83=VG5==O 48E0==O. @>2545==O A?5FV0;L=8E 70E>4V2,
B0:8E O: D>@A>20=89 4VC@57, 4V0;V7 01> 35<>?5@DC7VO, =5 A?@8ONBL ?@8A:>@5=>@30=V7:
28A>:>3> ABC?5=O 7207C20==O 7 1V;:0<8 V V=B5=A82=>
@07V ?>B5=V9=> B>:A8G=>3> ?5@54>7C20==O =5>1EV4=5 70AB>AC20==O 0:B82>20=>3>
2C3V;;O B0 520:C0FVN 2<8B8 H;C=>:).

>1VG=V @50:FVW.

0ABC?=V ?>1VG=V 5D5:B8 2;:NG0NBL @50:FVW, ?@> O:V ?>2V4<<O;>AO ?@8 :>@>B:> B@820;>
AC20==O ?@5?0@0BC @B>D5= B0/01> V=H8E ;V:0@AL:8E D>@< 48;:>D5=0:C.

I>:C A8AB5<8 :@>2V V ;VW A8AB5<8: B@<<1>F8B>?5=VO, ;59:>?5=VO, 0=5F8B>7.

I>:C VW A8AB5<8: 3V?5@GCB;82VABL, 0=0DV;0:B8G=V B0 0=0DV;0:B>W4=V @50:FVW (7>:@5<0 0@B5@V0;L=0 3V?>B5=7VO V H>:), 0=3V>=52@>B8G=89 =01@O: (7>:@5<0 =01@O: >1;8GGO). A8EVG=V @>7;048: 457>@VT=B0FVO, 45?@5AVO, 157A>==O, =VG=V :>H<0@8, 4@0BV2;82VABL, ?A8E>B8G=V @>7;048.

I>:C F5=B@0;L=>W =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O, A>;82VABL, ?0@5AB57VW, ?>@CH5==O ?0<OBV, AC4<8, 2V4GCBBO B@82>38, B@5<>@, 0A5?B8G=89 <5=V=3VB, A?>B2>@5==O A<0:>28E 2V4GCBV2, V=AC;LB.

I>:C >@30=V2 7>@C: 7>@>2V ?>@CH5==O, =5GVB:VABL 7>@C, 48?;>?VO.

I>:C >@30=V2 A;CEC B0 25AB81C;O@=>3> 0?0@0BC: 25@B83>, 472V= C 2CE0E, ?>@CH5==O A;CEC.

I>:C A5@F52>-AC48==>W A8AB5<8: 2V4GCBBO A5@F518BBO, 1V;L C 3@C4OE, A5@F520 =54>AB0B=VABL, V=D0@:B:0@40, 0@B5@V0;L=0 3V?5@B5=7VO, 20A:C;VB.

I>:C 48E0;L=>W A8AB5<8, >@30=V2 3@C4=>W :;VB:8 B0 A5@54>ABV==O: 0AB<0 (2;:NG0NG8 48A?=>5), ?=52<>=VB.

I>:C H;C=:>2>-.8H:>2>3> B@0:BC: =C4>B0, 1;N20==O, 4V0@5O, 48A?5?AVO, 014>

I>:C 35?0B>1V;V0@=>W A8AB5<8: ?V428I5==O @V2=O B@0=A02BO=8FO, ?>@CH5==O DC=:FVW ?5GV=:8, DC;L7 ?5GV=:8, ?5GV=:>20 =54>AB0B=VABL.

I>:C H:V@8 V ?V4H:V@=>W :;VB:>28=8: 28A8?0==O, :@>?82O=:0, 1C;L>7=V 28A8?0==O, 5:75<0, @ <=0 5@8B5<0, A8=4@< !BV25=A0-6>=A>=0, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7 (A8=4@< 09T;;0), 5:AD>;V0B82=89 45@<0B8B, 28?04V==O 2>;>AAO, D>B>A5=A81V;V70FVO, 0;5@3VG=0 ?C@?C@0, A25@1V6.

I>:C =8@>: B0 A5G>284V;L=8E H;OEV2: 70B@8AB@0 =8@:>20 =54>AB0B=VABL, 35<0BC@VO, ?@>B5W=C@VO, =5D@>B8G=89 A8=4@<, V=B5@AB8FV0;L=89 =5D@8B, <54C;O@=89 =5:@>7 =8@:8.

0=V :;V=VG=8E 4>A;V465=L B0 5?V45;>3VG=V 40=V A2V4G0BL ?@> ?V428I5=89 @878: B@> <1>B8G=8E CA:;04=5=L (=0?@8:;04, V=D0@:B:0@40 G8 V=AC;LB), ?>2O70=89 V7 70AB>AC20==O< 48:;>D5=0:C, 7>:@5<0 C 28A>:8E B5@0?52B8G=8E 4>70E (150 <3 =0 4>1C) B0 ?@8 B@820;>AC20==V.

"5@ABV. 3 @>:8.

#<>28 715@V30==O.

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

15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 10 B01;5B>: C 1;VAB5@V;

?> 10 B01;5B>: C 1;VAB5@V; ?> 3 1;VAB5@8 C ?0GFV V7 :0@B>=C;

?> 10 B01;5B>: C 1;VAB5@V; ?> 100 1;VAB5@V2 C :>@>1FV V7 :0@B>=C.

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

8@>1=8:.

@" «"5E=>;>3».

VAf57=0E>465==O28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

#:@0W=0, 20300, '5@:0AL:0 >1;.,