

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

"75
(RAPTEN 75)

!::04:

4VNG0 @5G>28=0: 48::>D5=0::
1 <; @>7G8=C 48::>D5=0:C =0B@VN 25 <3;
4>?>28=8: A?8@B 15=78;>289, =0B@VN <5B01VAC;LDVB(223), <0=VB (421), =0B@VN 3V4@>:A84,
?@>?V;5=3;V:>;L, 2>40 4;O V=T:FV9.

V:0@AL:0 D>@<0. >7G8= 4;O V=T:FV9.

\$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 B0 A?>@V4=5=V A?>;C:8. 8::>D5=0:..>4 ATC M01A B05.

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

>:070==O.

@5?0@0B ?@8 2=CB@VH=L><□O7>2>

- 70?0;L=8E B0 4535=5@0B82=8E D>@< @52<0B871>2>3> @52<0B87
- 3>AB@8E =0?04V2 ?>403@8;
- =8@:>2>W B0 1V;V0@=>W :>;V::
- 1>;N B0 =01@O:C ?VA;O B@02< V >?5@0FV9;
- BO6:8E =0?04V2

@5?0@0B ?@8 22545==V C 283;O4V 2=CB@VH=L>25==8E V=DC7V9 ?@87=0G5=89 4;O ;V:C20==O 01>
?@>DV;0:B8:8 ?VA;O>?5@0FV9=>3> 1>;N.

@>B8?>:070==O.

V4><0 3V?5@GCB;82VABL 4> 4VNG>W @5G>28=8,<5B01VAC;LDVBC 01> 4> 1C4L-O:8E V=H8E :>
=5=BV2 ?@5?0@0BC;

0;5@3VG=0 @50:FVO =0 V=HV =5AB5@>W4=V ?@>B870?0;L=V 70A>18 (), =0?@8::04

0F5B8;A0;VF8;>2C :8A;>BC, O:0 <>65 28@060B8AO 1@>=E>A?07<><, :@>?82O=:>N, 3>AB@8<
@8=VB><, ?>;V?0<8 =>A0 01> V=H8<8 0;5@3VG=8<8 A8<0<8;

0:B82=0 28@07:0 H;C=:0 01> :8H5G=8:C, :@>2>B5G0 01> ?5@D>@0FVO;

70?0;L=V 70E2>@N20==O :8H5G=8:C (=0?@8::04 E2>@>10 @>=0 01> 28@07:>289 :>;VB);

BO6:0 D>@<0 ?5GV=:>2>W =54>AB0B=>ABV (Child-Pugh ;:0AC !, F8@>7 ?5GV=:8 V 0AF8B);

?>@<8 =8@:>2>W =54>AB0B=>ABV (:;V@5=A :@50B8=V=C < 30 <;/E2);

70ABV9=0 A5@F520 =54>AB0B=VABL (NYHA II-IV);

VH5@>10 A5@FO C ?0FVT=BV2, O:V <ONBL AB5=>:0@4VN, ?5@5=5A5=89 V=D0@:B:0@40;

F5@51@>20A:C;O@=V 70E2>@N20==O C ?0FVT=BV2, O:V ?5@5=5A;8 V=AC;LB 01> <ONBL 5?V7>48
B@0=78B>@=8E VH5

70E2>@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).

?0FVT=B8 7 28A>:8< @878:>< @>728B:C ?VA;O>?5@0FV9=8E :@>2>B5G, =573>@B0==O :@>2V,

?>@CH5==O 35<>AB07C, 35<>?>5B8G=V ?>@CH5==O G8 F5@51@>20A:C;O@=V :@>2>B5GV.

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

030;L=0 @5:><5=40FVO 4>7C A;V4 ?V418@0B8 V=482V4C0;L=>, ?>G8=0NG8 7 @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.

@5?0@0B 0?B5= 75, @>7G8= 4;O V=T:FV9 =5 70AB>A>2C20B8 1V;LH5 2 4=V2; C @07V

=5>1EV4=>ABV ;V:C20==O <>6=0 ?@>4>268B8 V7 70AB>AC20==O< V=H8E ;V:0@AL:8E D>@<
(B01;5B:8 01> AC?>78B>@VW).

=CB@VH=L><O7>20 V=T:FVO
<5B>N ?>?5@5465==O ?>H:>465==O =5@2>28E 01> V=H8E B:0=8= C <O7>2>W V=T:FVW ?>B@V1=>
28:>=C20B8 =0ABC?=V ?@028;0.
>70 70728G09 AB0=>28BL >4=C 01C H;OE>< 3;81>:>W V=T:FVW C 25@E=V9 7>2=VH=V9 A5:B>@
25;8:>3> AV4=8G=>3><O70. # BO6:8E 28?04:0E (=0?@8::04 :>;V:8), 4>1>2C 4>7C <>6=0 71V;LH8B8 4>
42>E V=T:FV9 ?> 75 <3, 20B8 V=B5@20; C :V;L:0 3>48= (?> >4=V9 V=T:FVW 2 :>6=C AV4=8FN). #
O:>ABV 0;LB5@=0B828 >4=C 0 75 <3 <>6=0 :><1V=C20B8 7 V=H8<8 ;V:0@AL:8<8 D>@<0<8 4>
7030;L=>W <0:A8<0;L=>W 4>1>2>W 4>78 150 <3.
C<>20E =0?04C A2V4 >1<565=89 28?04:0<8 7 ?>G0B:>28< 70AB>AC20==O< >4=VTW 07C 22>48B8 ?@8
<>6;82>ABV >4@07C 6 ?VA;O 70AB>AC20==O AC?>78B>@VW2 ?> 100<3 C B>9 65 A0<89 45=L (?@8
=5>1EV4=>ABV). 030;L=0 4>1>20 4>70 =5 <0T ?5@528IC20B8 175 <3 C ?5@H89 45=L.

=CB@VH=L>25==V V=DC7VW
0?B5= 75 @>7G8= 4;O V=T:FV9, =5 A;V4 22>48B8 C 283;O4V 2=CB@VH=L>25==>W 1>;NA=>W
V=T:FVW.
57?>A5@54=L> ?5@54 ?>G0B:>< 2=CB@VH=L>25==>W V=DC7VW 0?B5= 75, 70;56=> 2V4
=5>1EV4=>W WW B@820;>ABV, A;V4 @>725AB8 C 100-500<; 0,9 % @>7G8=C =0B@VN E;>@84C 01>
5 % @>7G8=C 3;N:>78, 1CD5@87>20=>3> @>7G8=>< 1V:0@1>=0BC =0B@VN 4;O V=T:FVW (0,5<;
8,4 % @>7G8=C 01> 1 <; 4,2 % 01> 2V4?>2V4=89 >1T< V=H>W :>=F5=B@0FVW), I> 27O;8 7V I>9=>
2V4:@8B>3> :>=B59=5@0; 4>40B8 4> FL>3> @>7G8=C 24=VTW 0 0?B5= 75. 8:>@8AB>2C20B8 <>6=0
BV;L:8 ?@>7>@V @>7G8=8. /:I>C @>7G8=V T :@8AB0;8 01> >A04, 4;O V=DC7VW 9>3>
70AB>A>2C20B8 =5 <>6=0.

5:><5=4>20=V 420 0;LB5@=0B82=V @568<8 4>7C20==O ?@5?0@0BC 0?B5= 75 @>7G8=C 4;O
V=T:FV9. ;O ;V:C20==O ?>3> V BO6:>3> ?VA;O?5@0FV9=>3> 1>;N 75<3 =5>1EV4=> 22>48B8
157?5@5@2=> 2V4 30 E28;8= 4> 2 3>48=. # @07V =5>1EV4=>ABV ;V:C20==O <>6=0 ?>2B>@8B8
G5@57 :V;L:0 3>48=, 0;5 4>70 =5 <0T ?5@528IC20B8 150 <3 ?@>BO3>< 1C4L-O:>3> ?5@V>4C C 24
3>48=8.
;O ?@>DV;0:B8:8 ?VA;O?5@0FV9=>3> 1>;N G5@57 15 E2- 1 3>48=C ?VA;O EV@C@3VG=>3>
2B@CG0==O ?>B@V1=> 225AB8 =020=B06C20;L=C 4>7C 25-50 <3, ?VA;O FL>3> =5>1EV4=>
70AB>AC20B8 157?5@5@2=C V=DC7VN ?@81;87=> 5 <3/3>48=C 06 4> <0:A8<0;L=>W 4>1>2>W 4>78
150 <3.

>1VG=V @50:FVW.

0ABC?=V =51060=V 5D5:B8 2:;NG0NBL O28I0, ?>2O70=V 7 22545==O< ?@5?0@0BC 0?B5= 75
@>7G8=C 4;O V=T:FV9 B0/01> V=H8E ;V:0@AL:8E D>@< 48;:>D5=0:C 70 C<>2 :>@>B:>AB@>:>2>3> V
4>23>B@820;>3> 70AB>AC20==O.
=D5:FVW B0 V=207VW: 01AF5A C

I>:C A8AB5<8 :@>2>B2>@5==O: B@><1>F8B>?5=VO, ;59:>?5=VO, 0=5F8B>7.
I>:C VW A8AB5<8: 3V?5@GCB;82VABL, 0=0DV;0:B8G=0 B0 ?A524>0=0DV;0:B8G=0 @50:FVW
(2:;NG0NG8 3V?>B5=7VN B0 H>.); 0=3V>=52@>B8G=89 =01@O: (2:;NG0NG8 =01@O: >1;8GGO).
A8EVG=V @>7;048: 457>@VT=B0FVO, 45?@5AVO, V=A<=VO, =VG=V :>H<0@8, 4@0BV2;82VABL,
?A8EVG=V @>7;048.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O; A>;82VABL; ?0@5AB57VO,
?>@CH5==O ?0<OBV, AC4<8, B@82>6=VABL, B@5<>@, 0A5?B8G=89 <5=V=3VB, @>7;04 2V4GCBBO
A<0:C, V=AC;LB, ?>@CH5==O 2V4GCBBO ?@8 4>B8:C.

I>:C >@30=V2 7>@C: @>7;04 7>@C, 70BC<0=5==O 7>@C, 48?;>?VO.
I>:C >@30=V2 A;CEC B0 ;01V@8=BC: 25@B83>; 472V= C 2CE0E, ?>@CH5==O A;CEC.

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

5A?V@0B>@=V, B>@0:0;L=V B0 <54V0AB8=0;L=V ?>@CH5==O: 0AB<0 (2:;NG0NG8 48A?=>5),
1@>=E>A?07<; ?=52<>=VB.

I>:C B@02=>W A8AB5<8: =C4>B0, 1;N20==O, 4V0@50, 48A?5?AVO, 014>, E2>@>10 @>=0), 70?>@,
AB><0B8B, 3;>A8B, 3;>B:>289 @>7;04 ?>4V1=8E 4> 4V0D@03<8 V=B5AB8=0;L=8E AB@8:BC@,
?0=:@50B8B.

5?0B>1V;V0@=V @>7;048: 71V;LH5==O @V2=O B@0=A02BO=8FO, ?>@CH5==O DC=:FVW ?5GV=:8;
<8BBT289 35?0B8B, 35?0B>=5:@>7, ?5GV=:>20 =54>AB0B=VABL.

I>:C H:V@8 B0 ?V4H:V@=8E B:0=8=: 28A8?8; :@>?82O=:0; 1C;L>7=5 28A8?0==O, 5:75<0, 5@8B5<0, @<=0 5@8B5<0, @V7=V 2848 5@8B5<, 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, 2B@0B0 2>;>AAO, @50:FVO D>B>GCB;82>ABV, ?C@?C@0, 0;5@3VG=0 ?C@?C@0, A25@1V6.

I>:C =8@>: B0 A5G>282V4=8E H;OEV2: 3>AB@0 =8@>:20 =54>AB0B=VABL, 35<0BC@VO, ?@>B5W=C@VO, =5D@>B8G=89 A8=4@<, V=B5@AB8FV0;L=89 =5D@8B, =8@>:289 ?0?V;O@=89 =5:@>7.

030;L=V ?>@CH5==O B0 ?>@CH5==O C @50:FVO C , 01AF5A C

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), ?>2 O70=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@54>7C20==O.

/8<8. "8?>20 ;;V=VG=0 :0@B8=0 =0A;V4:V2 ?5@54>7C20==O 48:;>D5=0:C 2V4ACB=O. 5@54>7C20==O <>65 A?@8G8=8B8 B0:V A8<8 O: 1;N20==O, 30AB@>V=B5AB8=0;L=0 :@>2>B5G0, 4V0@50, 70?0 <>@>G5==O, 472V= C 2CE0E 01> AC4<<8. # 28?04:C B06:>3> >B@CT==O <>6;820 3>AB@0 =8@>:20 =54>AB0B=VABL B0 C@065==O ?5GV=:8.

V:C20==O. V:C20==O 3>AB@>3> >B@CT==O A:;040TBLAO C ?5@HC G5@3C 7 ?V4B@84V2 B0 A8 <0B8G=>3> ;V:C20==O. V4B@848 B0 A8<0B8G=5 ;V:C20==O =5>1EV4=V 4;O CAC=5==O B0:8E CA:;04=5=L O: 3V?>B5=7VO, =8@>:20 =54>AB0B=VABL, AC4<<8, 30AB@>V=B5AB8=0;L=V ?>@CH5==O B0 ?@83=VG5==O 48E0==O.

A>1;82V 70E>48, B0:V O: D>@A>20=89 4VC@57, 4V0;V7 01> 35<>?5@DC7VO, =5 <>6CBL 30@0=BC20B8 282545==O =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2 C=0A;V4>: WE 28A>:>3> 7207C20==O 7 ?@>B5W=0<8 ?;07<8 :@>2V B0 V=B5=A82=8< <5B01>;V7<>

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

03VB=VABL

0?B5= 75 =5 A;V4 70AB>A>2C20B8 ?V4 G0A ?5@H8E 42>E B@8<5AB@V2 203VB=>ABV, 70 28=OB:<< B8E 28?04:V2, :>;8 ?>B5=8V9=0 :>@8ABL 4;O <0B5@V ?5@528ICT @878: 4;O ?;>40. /: V 7 V=H8<8 =5AB5@>W4=8<8 ?@>B870?0;L=8<8 70A>10<8, 70AB>AC20==O ?V4 G0A B@8<5AB@C 203VB=>ABV ?@>B8?>:070=5 2=0A;V4>: <>6;82>3> @>728B:C 2V4ACB=>ABV A:>@>G5==O <0B:8 B0 /01> ?5@54G0A=>3> 70:@8BBO ductus arteriosus.

5@V>4 3>4C20==O 3@C44N

/: V V=HV =5AB5@>W4=V ?@>B870?0;L=V 70A>18, 48:;>D5=0: ?@>=8:0T C <0B5@8=AL:5 <>:>: C =525;8:V9 :V;L:>ABV."0:8< G8=><, I>1 C=8:=CB8 =51060=>3> 2?;82C =0 =5<>2;O, 0?B5= 75 =5 A;V4 70AB>A>2C20B8 C ?5@V>4 3>4C20==O 3@C44N.

§5@B8;L=VABL

/: V V=HV =5AB5@>W4=V ?@>B870?0;L=V 70A>18, 0?B5= 75 <>65 2?;8=CB8 =0 D5@B8;L=VABL 6V=:8. @5?0@0B =5 @5:<<5=4CTBLAO 6V=:0<, O:V ?;0=CNBL 70203VB=VB8. V=:8, O:V <0NBL CA:;04=5==O 7 70?;V4=5==O< 01> BV, EB> ?@>E>482 >1AB565==O 2=0A;V4>: V=D5@B8;L=>ABV, <0NBL ?@8?8=8B8 70AB>AC20==O ?@5?0@0BC.

VB8.

#=0A;V4>: 7=0G=>3> 2?;82C ?@5?0@0BC 0?B5= 75 C 40=V9 ;V:0@AL:V9 D>@7G8=C 4;O V=T:FV9 =5 A;V4 70AB>A>2C20B8 4VBO

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

@8 70AB>AC20==V 2AVE =5AB5@>W4=8E ?@>B870?0;L=8E 70A>1V2 () H;C=:>2>-.8H:>20 :@>2>B5G0, 28@07:8 01> ?5@D>@0FVW <>6CBL 1CB8 ;5B0;L=8<8 V <>6CBL 28=8:0B8 C 1C4L-O:89 ?5@V>4 G0AC 2?@>4>26 ;V:C20==O, 7 01> 157 ?>?5@546C20;L=8E A8 A5@9>7=8E H;C=:>2>-.8H:>28E O28I 2 0=0<=57V. # E2>@8E ;VB=L>3> 2V:C FV O28I0<0NBL 70728G09 1V;LH A5@9>7=V =0A;V4:8. # @07V 28=8:=5==O H;C=:>2>-.8H:>2>W :@>2>B5GV C E2>@8E, O:V >B@81EV4=> 2V4 A=CT ?V428I5=89 @878: B@<1>B8G=8E A5@F52>-AC48==8E B0 F5@51@>20A:C;O@=8E CA:;04=5=L V7 ?52=8<8 A5;5:B82=8<8 V=3V1VB>@0<8 &-2. >B5?5@ =52V4<<, G8 F59 @878: C ?@OABV &-1 / &-2 A5;5:B82=>ABV >:@5<8E . 5<0T =0 40=89 G0A 4>ABC?=8E 40=8E I>4> B@820;>3> ;V:C20==O<0:A8

<0;L=>N 4>7>N 48;:>D5=0:C. >>B@8<0==O B0:8E 40=8E =5>1EV4=> 74V9A=N20B8 @5B5;L=C >FV=:C
A?V22V4=>H5==O @878:C V :>@8ABV 70AB>AC20==O 48;:>D5=0:C ?0FVT=B0< V7 ;;V=VG=>
?V4B25@465=>N VH5N E2>@>1>N A5@FO, F5@51@>20A:C;O@=8<8 ?>@CH5==O<8, >;;N7V9=8<8
70E2>@N20==O<8 ?5@8D5@8G=8E 0@B5@V9 01> 7=0G=8<8 D0:B>@0<8 @878:C (=0?@8;:04
0@B5@V0;L=0 3V?5@B5=7VO, 3V?5@;V?V45289 4V015B, ?0;V==O). # 7207:C 7 @878:>< ?>28==0
1CB8 70AB>A>20=0 =09=86G0 5D5:B82=0 4>70 ?@>BO3>< =09:>@>BH>3> :C@AC ;V:C20==O.
8@:>2V 5D5:B8 2;:NG0NBL 70B@8< B0/01> 0@B5@V0;L=>N 3V?5@B5=7VTN. ">D5=0: A;V4
70AB>A>2C20B8 V7 70AB5@565==O< ?0FVT=B0< V7 A5@F52>N 48ADC=:FVTN B0 V=H8<8 AB0=0<8,
O:V ?@872>4OBL 4> 70B@86 ?>:070=0 ?0FVT=B0<, O:V 70AB>A>2CNBL 4VC@5B8:8 01> AC?CB=L>
V=3V1VB>@8 \$, 01> O:V <0NBL ?V428I5=89 @878: 3V?>2>;5
7207:C V7 70AB>AC20==O<, 2;:NG0NG8 48;:>D5=0:, A?>AB5@V30;8AO A5@9>7=V @50:FVW 7 1>:C
H:V@8, 450:V 7 =8E ;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 40=8E @50:FV9 C ?0FVT=V2
VA=CT =0 ?>G0B:C :C@AC ;V:C20==O, C 1V;LH>ABV 28?04:V2 ?>O20 F8E @50:FV9 2V41C20TBLAO C
<560E ?5@H>3> 0AB>AC20==O 48;:>D5=0:C A;V4 ?@8?8=8B8 ?@8 ?5@HV9 ?>O2V 28A8?0=L =0
H:V@V, C@065=L A;87>28E >1>;>=: 01> 1C4L-O:8E V=H8E >7=0: 3V?5@GCB;82>ABV.
/: V ?@8 70AB>AC20==V V=H8E , @V4:> 157 ?>?5@54=L>W 5:A?>78FVW 48;:>D5=0:C <>6CBL B0:>6
28=8:=CB8 0;5@3VG=V @50:FVW, C B>W4=V. 5B01VAC;LDVB C @>7G8=V 4;O V=T:FV9 B0:>6<>65
?@8725AB8 4> >:@5<8E BO6:8E @50:FV9 3V?5@GCB;82>ABV B0 1@>=E>A?07
<>6CBL 71V;LH8B8 @878: 28=8:=5==O A5@9>7=8E A5@F52>-AC48==8E B@<1>B8G=8E O28I,
V=D0@:BC :0@40 B0 V=AC;LBC, O:V <>6CBL 28O28B8AO ;5B0;L=8<8, C 7207:C 7 G8< 0?B5= 75 =5
@5:><5=4CTBLAO 70AB>A>2C20B8 4;O ;V:C20==O ?VA;O>?5@0FV9=>3> 1>;N ?V4 G0A >?5@0FVW 7
0>@B>:>@>=0@=>3> HC=BC20==O.
/: V V=HV , 0?B5= 75, 7024O:8 A2>W< D0@<0:>48=0
@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, :C@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 48;:>D5=0:C <>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 C ?0FVT=V2 AB0@H5 65 @>:V2.
□0AB5@565==O
030;L=V
!;V4 C=8:0B8 70AB>AC20==O ?@5?0@0BC 7 A8AB5<=8<8 , 2;:NG0NG8 A5;5:B82=V V=3V1VB>@8 &-2,
G5@57 2V4ACB=VABL 1C4L-O:>W A8=5@3VG=>W :>@8ABV V<>6;82>ABV @>728B:C 4>40B:>28E
>1VG=8E 5D5:BV2.
!;V4 1CB8 >15@56=8<8 ?@8 ?@87=0G5==V ?@5?0@0BC >A>10< ;VB=L>3> 2V:C. >:@5<0, 4;O ;N459
;VB=L>3> 2V:C 7V A;01:8< 74>@>2O< B0 4;O ?0FVT=V2 V7 =87L:8< ?>:07=8:<< <0A8 BV;0 @5:>
<5=4CTBLAO 70AB>A>2C20B8 =09=86GV 5D5:B82=V 4>78.
AB<0 2 0=0<=57V
E2>@8E =0 1@>=EV0;L=C 0AB==89 0;5@3VG=89 @8=VB, =01@O: A;87>2>W >1>;>=:8 =>A0 (B>1B>
=070;L=V ?>;V?8), E@>=VG=V >1AB@C:B82=V 70E2>@N20==O ;535=L 01> E@>=VG=V V=D5:FVW
48E0;L=8E H;OEV2 (>A>1;82> ?>2O70=8E 7 0;5@3VG=8<8 ?>4V1=8<8 4> @8=VBV2 A8<0<8) G0ABVH5
70 V=H8E 28=8:0NBL @50:FVW =0 AE>6V =0 703>AB@5==O 0AB<8 (O:V B0:>6 ?>2O70=V 7 ?5@5=>A8
W 0AB<8), =01@O: 2V=:5 01> :@>?82O=:0. # 7207:C 7 F8< B0:8< E2>@8< @5:><5=4>20=V A?5FV0;L=V
70AB5@56=V 70E>48 (3>B>2=VABL 4> =040==O =52V4;:04=>W 4>?>>38). &5 B0:>6 AB>ACTBLAO
E2>@8E =0 0;5@3VN =0 V=HV @5G>28=8, =0?@8;:04 7V H:V@=8<8 @50:FVO<8, A25@1565< 01>
:@>?82O=:>N.
A>1;82V 70AB5@565==O @5:><5=4CNBLAO C 28?04:C, :>;8 0?B5= 75 70AB>A>2CNBL
?0@5=B5@0;L=> ?0FVT=B0< 7 1@>=EV0;L=>N 0AB<>N, >A:V;L:8 A8<8 <>6CBL 703>AB@N20B8AO.
?;82 =0 B@02=89 B@0:B
/: V ?@8 70AB>AC20==V V=H8E , ?@8 ?@87=0G5==V ?@5?0@0BC 0?B5= 75 ?0FVT=B0< V7 A8<0<8, I>
A2V4G0BL ?@> ?>@CH5==O 7 1>:C B@02=>3> B@0:BC ("") 01> 7 0=0<=57<<, I> ?5@5410G0T
=0O2=VABL 28@07:8 H;C=:0 01> :8H5G=8:C, :@>2>B5GV 01> ?5@D>@0FVW, >1>2O7:>28< T
<548G=89 =03;04 V >A>1;820 >15@56=VABL. 878: 28=8:=5==O :@>2>B5GV C "" 71V;LHCTBLAO 7
?V428I5==O< 4>78 V C E2>@8E 7 28@07:>N 2 0=0<=57V, >A>1;82> 7 CA;:04=5==O<8 C 283;04V

:@>2>B5GV 01> ?5@D>@0FVW B0 C ;N459 ;VB=L>3> 2V:C.
)>1 7=878B8 @878: B>:A8G=>3> 2?;82C =0 "" C ?0FVT=BV2 7 28@07:>N 2 0=0<=57V, >A>1;82> 7
CA:;04=5==O<8 C 283;04V :@>2>B5GV 01> ?5@D>@0FVW B0 C ;N459 ;VB=L>3> 2V:C, ;V:C20==O
A;V4 @>7?>G8=0B8 B0 ?V4B@8
;O B0:8E ?0FVT=BV2, 0 B0:>6 E2>@8E, O:V ?>B@51CNBL AC?CB=L>3> 70AB>AC20==O ;V:0@AL:8E
70A>1V2, I> 78 0F5B8;A0;VF8;>2>W :8A;>B8 (!) 01> V=H8E ;V:0@AL:8E 70A>1V2, O:V, 9<>2V@=>,
?V428ICNBL @878: =51060=>W 4VW =0 "", A;V4 @>73;O=CB8 ?8B0==O ?@> 70AB>AC20==O :>
<1V=>20=>W B5@0?VW 7 70AB>AC20==O< 70E8A=8E 70A>1V2 (=0?@8:;04 V=3V1VB>@V2
?@>B>==>3> =0A>A0 01> ?@>AB>;C).
0FVT=B8 7V H;C=:>2>.:8H:>2>N B>:A8G=VABN 2 0=0<=57V, >A>1;82> ;VB=L>3> 2V:C,<0NBL ?>2V4>
<;OB8 ?@> 1C4L-O:V =5728G=V 014> <>6CBL ?V428I8B8 @878: 28@07:8 01> :@>2>B5GV, B0:V O:
A8AB5<=V :>@B8:>AB5@>W48, 0=B8:>03C;O=B8, 0=B8B@><1>B8G=V 70A>18 01> A5;5:B82=V
V=3V1VB>@8 72>@>B=>3> 70E>;5==O A5@>B>=V=C.
0?B5= 75 =5>1EV4=> 7 >15@56=VABN ?@87=0G0B8 E2>@8<, 2 0=0<=57V O:8E T 70?0;L=V
70E2>@N20==O :8H5G=8:C, B0:V O: E2>@>10 @>=0 01> =5A?5F8DVG=V 28@07:>2V :>;VB8 B0
2AB0=>2;N20B8 @5B5;L=89 <548G=89 =03;04 B0 2V4?>2V4=V 70AB5@56=V 70E>48 C 7207:C 7 B8<,
I> WE AB0= <>65 703>AB@N20B8AO.
?:82 =0 ?5GV=:C
5B5;L=89 <548G=89 =03;04 ?>B@V15= C 28?04:C, :>;8 0?B5= 75 ?@87=0G0TBLAO ?0FVT=B0< 7
C@065=>N DC=:FVTN ?5GV=:8, >A:V;L:8 WE AB0= <>65 703>AB@8B8AO.
/: V ?@8 70AB>AC20==V V=H8E, @V25=L >4=>3> V 1V;LH5 ?5GV=:>28E 5=780?B5= 75,
?@87=0G0TBLAO @53C;O@=89 =03;04 70 DC=:FVO<8 ?5GV=:8 C O:>ABV 70AB5@56=8E 70E>4V2.
/:I> ?>@CH5==O DC=:FVW ?5GV=:8 715@V30NBLAO 01> ?>3V@HCNBLAO, O:I> :;V=VG=V >7=0:8
01> A8<8 <>6CBL 1CB8 ?>2O70=V 7 ?@>3@5ACNG8<8 70E2>@N20==O<8 ?5GV=:8 01> O:I>
A?>AB5@V30NBLAO V=HV ?@>O28 (=0?@8:;04 5>78=>DV;VO, 28A8?0==O), 70AB>AC20==O
?@5?0@0BC 0?B5= 75 A;V4 ?@8?8=8B8. 5@51V3 70E2>@N20=L, B0:8E O: 35?0B8B8, <>65 ?@>E>48B8
157 ?@>4@><0;L=8E A8
0AB5@565==O =5>1EV4=V C 28?04:C, :>;8 0?B5= 75 70AB>A>2C20B8 ?0FVT=B0< 7 ?5GV=:>2>N
?>@DV@VTN G5@57 V<>2V@=VABL ?@>2>:0FVW =0?04C.
?:82 =0 =8@:8
A:V;L:8 ?@8 ;V:C20==V ?>2V4<;O;>AO ?@> 70B@8A>1;82C C203C A;V4 ?@84V;8B8 E2>@8< V7
?>@CH5==O< DC=:FVW A5@FO 01> =8@>: (C B. G. DC=:FV>=0;L=>N =8@:>2>N =54>AB0B=VABN =0
B;V 3V?>2>;5B8G=>3> A8=4@>2G0:>2>W =5D@>?0B8VW B0 45:>20=>3> F8@>7C ?5GV=:8),
0@B5@V0;L=C 3V?5@B5=7VTN 2 0=0<=57V, E2>@8< ;VB=L>3> 2V:C, E2>@8<, O:V >B@8W
?@8G8=8, =0?@8:;04 4> 01> ?VA;O A5@9>7=>3> EV@C@3VG=>3> 2B@CG0==O. #B0:8E 28?04:0E C
O:>ABV 70AB5@56=8E 70E>4V2 @5:><5=4CTBLAO <=VB>@8=3 =8@:>2>W DC=:FVW. @8?8=5==O
B5@0?VW 70728G09 7C<>2;NT ?>25@=5==O 4> AB0=C, O:89 ?5@54C202 ;V:C20==N.
?:82 =0 35<0B>;>3VG=V ?>:07=8:8
@8 B@820;>AC20==V ?@5?0@0BC, O: V V=H8E, @5:><5=4CTBLAO <=VB>@8=3 0=0;V7C :@>2V.
/: V V=HV, 0?B5= 75 <>65 B82> ?@83=VGC20B8 03@530FVN B@><1>F8BV2. !;V4 @5B5;L=>
=03;040B8 70 E2>@8<8 7 ?>@CH5==O<8 35<>AB07C.

**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.**

0FVT=B8, C O:8E ?V4 G0A ;V:C20==O ?@5?0@0B< 0?B5= 75 A?>AB5@V30NBLAO ?>@CH5==O
7>@C, 70?0<>@>G5==O, 25@B83>, A>=:82VABL 01> V=HV ?>@CH5==O 7 1>:C F5=B@0;L=>W
=5@2>2>W A8AB5<8, <0NBL CB@8B@0=A?>@B< B0 @>1>B8 7 <5E0=V7<0<8.

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

86G5 =02545=V 270T<>4VW, I> A?>AB5@V30;8AO V7 70AB>AC20==O< ?@5?0@0BC 0?B5= 75,
@>7G8=C 4;O V=T:FV9 B0/01> V=H8E ;V:0@AL:8E D>@< 48:;>D5=0:C.
V BV9. 0 C<>2 >4=>G0A=>3> 70AB>AC20==O 48:;>D5=0: <>65 ?V428I8B8 :>=F5=B@0FVW ;VBVN C
?;072V. 5:>5=4CTBLAO <=VB>@8=3 @V2=V2 ;VBVN C A8@>20BFV :@>2V.
83>:A8=. 0 C<>2 >4=>G0A=>3> 70AB>AC20==O 48:;>D5=0: <>65 ?V428I8B8 :>=F5=B@0FVW
483>:A8=C C ?;072V. 5:>5=4CTBLAO <=VB>@8=3 @V2=V2 483>:A8=C C A8@>20BFV :@>2V.
VC@5B8:8 B0 0=B83V?5@B5=782=V 70A>18. !: V V=HV, AC?CB=T 70AB>AC20==O 48:;>D5=0:C 7
4VC@5B8:0<8 01> 0=B83V?5@B5=782=8<8 70A>10<8 (=0?@8:;04 15B0-1;>:0B>@0<8, V=3V1VB>@0<8

0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC (\$) <>6CBL ?@8725AB8 4> 7=865==O WE
0=B83V?5@B5=782=>3> 2?;82C. "0:8< G8=><, ?>4V1=C :><1V=0FVN A;V4 70AB>A>2C20B8 7
70AB5@565==O<, 0 ?0FVT=B8, >A>1;82> >A>18 ;VB=L>3> 2V:C, ?>28==V ?5@51C20B8 ?V4 @5B5;L=8
<=03;O4>< I>4> 0@B5@V0;L=>3> B8A:C. 0FVT=B8 <0NBL >B@8<5=4CTBLAO B0:>6 <=>VB>@8=3
=8@:>2>W DC=:FVW ?VA;O ?>G0B:C AC?CB=L>W B5@0?VW B0 =0 @53C;O@=V9 >A=>2V ?VA;O
=5W, >A>1;82> I>4> 4VC@5B8:V2 B0 V=3V1VB>@V2 \$ C=0A;V4>: 71V;LH5==O @878:C
=5D@>B>:A8G=>ABV. !C?CB=T ;V:C20==O 7 ?@5?0@0B0<8 :0;VN <>65 1CB8 ?>2O70=5 7V
71V;LH5==O< @V2=V2 :0;VN C A8@>20BFV :@>2V, I> 28<030T ?5@51C20==O E2>@8E ?V4 ?>ABV9=8
< :>=B@>;5

=HV B0 :>@B8:>AB5@>W48. !C?CB=T 22545==O 48;:>D5=0:C B0 V=H8E A8AB5<=8E 01>
:>@B8:>AB5@>W4V2 <>65 ?V428I8B8 G0AB>BC ?>1VG=8E @50:FV9 7 I>:C ""
=B8:>03C;O=B8 B0 0=B8B@><I>B8G=V 70A>18. 5:><5=4CTBLAO 268B8 70AB5@56=V 70E>48,
>A:V;L:8 AC?CB=T 22545==O <>65 ?V428I8B8 @878: :@>2>B5GV. %>G0 ;V=VG=V 4>A;V465==O =5
A2V4G0BL ?@> 2?;82 48;:>D5=0:C =0 0:B82=VABL 0=B8:>03C;O=BV2, VA=CNBL >:@571V;LH5==O
@878:C :@>2>B5GV C ?0FVT=BV2, O:V >B@8D5=0: B0 0=B8:>03C;O=B8 >4=>G0A=>. "><5=4>20=89
@5B5;L=89 <=>VB>@8=3 B0:8E ?0FVT=BV2.
!5;5:B82=V V=3V1VB>@8 72>@>B=>3> 70E>?;5==O A5@>B>=V=C (SSRIs). !C?CB=T 22545==O
A8AB5<=8E B0 SSRIs <>65 ?V428I8B8 @878: :@>2>B5GV C B@02=>
=B84V015B8G=V ?@5?0@0B8. ;V=VG=V 4>A;V465==O ?>:070;8, I> 48;:>D5=0: <>6=0 70AB>A>2C20B8
@07>< V7 ?5@>@0;L=8<8 0=B84V015B8G=8<8 70A>10<8 157 2?;82C =0 WE ;V=VG=C 4VN. 4=0: 2V4>
:@53;V:57C20==O 0=B84V015B8G=8E 70A>1V2 ?V4 G0A ;V:C20==O 48;:>D5=0:>B@51CNBL
<=>VB>@8=3C @V2=V2 3;N:>78 C :@>2V, I> T 70AB5@56=8< 70E>4>< ?V4 G0A AC?CB=L>W
B5@0?VW.

>;5AB8?>; B0 E>;5AB8@0 4=>G0A=5 70AB>AC20==O 48;:>D5=0:C B0 :>;5AB8?>;C 01> E>;5AB8@0 %
B0 60 % 2V4?>2V4=>. @5?0@0B8 A;V4 ?@89<0B8 7 V=B5@20;>< C :V;L:0 3>48=.

@5?0@0B8, O:V AB8@5?0@0B8, O:V AB8

5B>B@5:A0B. @8 22545==V <5=H =V6 70 24 3>48=8 4> 01> ?VA;O ;V:C20==O<5B>B@5:A0B>< @5:>
<5=4CTBLAO 1CB8 >15@56=8<8, >A:V;L:8 <>6CBL 7@>AB0B8 :>=F5=B@0FVW <5B>B@5:A0BC 2
:@>2V V 71V;LHC20B8AO B>:A8G=VABL FVTW @5G>28=8.

?>A?>@8= B0 B0:@>;V. 8;:>D5=0:, O: V V=HV , <>65 71V;LHC20B8 =5D@>B>:A8G=VABL
F8;:>A?>@8=C G5@57 2?;82 =0 ?@>AB03;0=48=8 =8@>:. "0:89 @878: 28=8:0T ?@8 ;V:C20==V B0:@>;V<
. # 7207:C 7 F8< 9>3> A;V4 70AB>A>2C20B8 2 =86G8E 4>70E, =V6 C E2>@8E, O:V F8;:>A?>@8= =5
>B@8

=B810:B5@V0;L=V EV=>;>=8. A=CNBL >:@54> AC4>, O:V <>6CBL 1CB8 @57C;LB0B><
AC?CB=L>3> 70AB>AC20==O EV=>;>=V2 B0 .

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

\$0@<0:>48=0

0?B5= 75 D5=0: =0B@VN, =5AB5@>W4=C A?>;C:C 7 28@065=8<8 ?@>B8@52<0B8G=8<8,
?@>B870?0;L=8<8, 7=51>;N20;L=8<8 B0 60@>7=86C20;L=8<8 2;0AB82>ABO<8. @83=VG5==O
1V>A8=B57C ?@>AB03;0=48=V2, O:5 1C;> ?@>45<=>AB@>20=5 C 5:A?5@8<5=B0E, 22060TBLAO
>A=>2=8< <5E0=V7<<< 9>3> 4VW. @>AB03;0=48=8 2V4V3@0NBL 206;82C @>;L C 28=8:=5==V
70?0;5==O, 1>;N B0 ?@>?0A=8FV.

@8 @52<0B8G=8E 70E2>@N20==OE ?@>B870?0;L=V B0 7=51>;N20;L=V 2;0AB82>ABV ?@5?0@0BC
>1C<>2;NNBL ;V=VG=C 2V4?>2V4L, O:0 E0@0:B5@87CTBLAO 28@065=8< 7=8:=5==O< >7=0: B0 A8
;N C AB0=V A?>:>N B0 ?V4 G0A @CEC, 2@0=VH=L>W @83V4=>ABV B0 =01@O:C AC3;>1V2, B0:>6 ?>
:@0I5==O DC=:FV9.

0?B5= 75 740B5= ?>A8;8B8 28@065=89 7=51>;N20;L=89 2?;82 =0 ?>;V =5@52<0B8G=>3> ?>E>465==O
?@>BO3>< 15-30 E2.

0?B5= 75 ?@>45<=>AB@C202 B0:>6 ACBBT289 2?;82 =0 =0?048

@8 ?>ABB@02<0B8G=8E B0 ?VA;O>?5@0FV9=8E AB0=0E V7 =0O2=VABN 70?0;5==O 0?B5= 75 H284:>
?>;53HCT A?>=B0==V 1>;V B0 1>;V ?V4 G0A @CEC V 7<5=HCT =01@O:8, A?@8G8=5=V 70?0;5==O<
B0 @0=0<8.

/I> ?@5?0@0B 70AB>A>2C20B8 >4=>G0A=> 7 ?>V>W4=8<8 7=51>;N20;L=8<8 70A>10<8 4;O 7=OBBO
?VA;O>?5@0FV9=>3> 1>;N, 0?B5= 75 ACBBT2> 7<5=HCT WE =5>1EV4=VABL.

0?B5= 75, @>7G8= 4;O V=T:FV9 2 0A>1;82> =5>1EV4=89 4;O ?>G0B:C ;V:C20==O 70?0;L=8E B0
4535=5@0B82=8E @52<0B8G=8E E2>@>1 B0 1>;L>2>3> AB0=C 2=0A;V4>: 70?0;5==O =5@52
<0B8G=>3> ?>E>465==O.

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

IA>@IFVO.

VA;O 22545==O 75 <3 48.;>D5=0:C H;OE>< 2=CB@VH=L><O7>2>W V=T:FVW 01A>@1FVO

?>G8=0TBLAO =5309=>, 0 A5@54=V <0:A8<0;L=V :=F5=B@0FVW C ?;07 AB0=>2;OBL ?@81;87=> 2,5
3@0