

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

>@VAB0®
(Lorista®)

!;:04:

4VNG0 @5G>28=0: 1 B01;5B:0

4>?>28=8: F5;0:B>70 (78 <=>3V4@0B B0 F5;N;>7C ?>@>H:>?>4V1=C), :@>E<0;L :C:C@C470=89,
:@>E<0;L ?@565;0B8=V7>20=89, F5;N;>70 :@8AB0;VG=0, :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89,
<03=VN AB50@0B, 3V?@>5;>70, B0;L.; ?@>?V;5=3;V:>;L, B8B0=C 4V>:A84 (E 171), 10@2=8:
EV=>;V=>289 6>2B89 (104) ;8H5 4;O B01;5B>: ?> 12,5 <3 B0 25 <3.

V:0@AL:0 D>@<0. "01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N.

\$0@<0:>B5@0?52B8G=0 3@C?0. @>ABV ?@5?0@0B8 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C
II.

>4 " ! !09! 01.

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

>:070==O.

V:C20==O 5A5=FV0;L=>W 3V?5@B5=7VW C 4>@>A;8E, 0 B0:>6 C 4VB59 2V:> 2V4 6 @>:V2.

V:C20==O 70E2>@N20==O =8@>: C 4>@>A;8E ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN B0
FC:@>28< 4V015B>< B8?C 7 ?@>B5W=C@VTN ≥ 0,5 3/4>1C O: G0AB8=0 0=B83V?5@B5=782=>W
B5@0?VW.

V:C20==O E@>=VG=>W A5@F52>W =54>AB0B=>ABV (C ?0FVT=BV2 2V:> 2V4 60 @>:V2), :>;8
70AB>AC20==O V=3V1VB>@V2 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC (\$) 22060TBLAO =5
<>6;828< 7 ?@8G8=8 =5ACABV, >A>1;82> ?@8 :0H;V, 01> ?@>B8?>:070=5. 0FVT=BV2 V7 A5@F52>N
=54>AB0B=VABN, AB0= O:8E AB01V;V7C202AO ?@8 70AB>AC20==V V=3V1VB>@C \$, =5 A;V4
?5@52>48B8 =0 ;V:C20==O ;>70@B0=>3> H;C=>G:0 ?>28==0 AB0=>28B8 ≤ 40 %, AB0=<0T 1CB8
;;V=VG=> AB01V;L=8<, B0:>6 ?0FVT=B>2V A;V4 4>B@82;5=>3> @5684> E@>=VG=>W A5@F52>W
=54>AB0B=>ABV.

=865==O @878:C @>728B:C V=AC;LBC C 4>@>A;8E ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN
V 3V?5@B@>DVTN ;V2>3> H;C=>G:0, I> 4>:C<5=B0;L=> ?V4B25@465=> 70 4>?><>3>N .

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> ;>70@B0=C 01> 4> 1C4L-O:>3> V=H>3> :>5=B0 ?@5?0@0BC.

03VB=V 01> 6V=:8, O:V ?;0=CNBL 70203VB=VB8 (482. @>74V; «0AB>AC20==O C ?5@V>4

203VB=>ABV 01> 3>4C20==O 3@C44N»). "06:V ?>@CH5==O DC=:FVW ?5GV=:8. 4=>G0A=5

70AB>AC20==O 7 0;VA:V@5=> ?0FVT=B0< 7 FC:@>28< 4V015B>< 01> ?>@CH5==O< DC=:FVW

=8@>: ((\$ <60 <;/E2/1,73<2) (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O» B0 «70T<>4VO 7 V=H8<8

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

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

"01;5B:8 ;>70@B0=C A;V4 70?820B8 A;;O=:>N 2>48.

0AB>AC20==O ?@5?0@0BC =5 70;568BL 2V4 ?@89>

@B5@V0;L=0 3V?5@B5=7VO

0728G09 ?>G0B:>20 V ?V4B@870 4;O 1V;LH>ABV ?0FVT=BV2 AB0=>28BL 50<3 ?@5?0@0BC 1 @07 =0

4>1C (1 B01;5B:0 >@VAB8 50 <3). 0:A8<0;L=89 0=B83V?5@B5=782=89 5D5:B 4>AO30TBLAO =0

3-6 B8645=L 2V4 ?>G0B:C ;V:C20==O. ;O 45O:8E ?0FVT=BV2 <>65 28O28B8AO A?@8OB;82VH8<

?V428I5==O 4>78 ?@5?0@0BC 4> 100 <3 1 @07 =0 4>1C (2@0=V).

>@VABC <>6=0 70AB>A>2C20B8 C ?>T4=0==V 7 V=H8<8 0=B83V?5@B5=782=8<8 ?@5?0@0B0<8,

>A>1;82> 4VC@5B8:0<8 (=0?@8;;04, 3V4@>E;>@BV0784><).

0FVT=B8 7 0@B5@V0;L=>N 3V?5@B5=7VTN B0 FC:@>28< 4V015B>< B8?C 7 ?@>B5W=C@VTN ≥ 0,5

3/4>1C

0728G09 ?>G0B:>20 4>70 AB0=>28BL 50 <3 (1 B01;5B:0 >@VAB8) 1 @07 =0 4>1C. >7C <>6=0
71V;LH8B8 4> 100 <3 1 @07 =0 4>1C 70;56=> 2V4 B>3>, O:8<8 T ?>:07=8:8 0@B5@V0;L=>3> B8A:C
G5@57 1 G0B:C ;V:C20==O. >@VABC <>6=0 70AB>A>2C20B8 7 V=H8<8 0=B83V?5@B5=782=8<8
?@5?0@0B0<8 (=0?@8::04 4VC@5B8:0<8, 1;>:0B>@0<8 :0;LFVT28E :0=0;V2, 1;>:0B>@0<8 α- 01> β-
@5F5?B>@V2 B0 ?@5?0@0B0<8 F5=B@0;L=>W 4VW), 0 B0:>6 7 V=AC;V=<< B0 V=H8<8 3V?>3;V:5
!5@F520 =54>AB0B=VABL
0728G09 ?>G0B:>20 4>70 >@VAB8 C ?0FVT=BV2 V7 E@>=VG=>N A5@F52>N =54>AB0B=VABN
AB0=>28BL 12,5 <3 1 @07 =0 4>1C. /: ?@028;>, 4>70 B8B@CTBLAO 7 B86=528< V=B5@20;>< (0 A0<5:
12,5 <3 =0 4>1C, 25 <3 =0 4>1C, 50 <3 =0 4>1C) 4> 728G09=>W ?V4B@8W 4>78 50 <3 (1 B01;5B:0
>@VAB8)
1 @07 =0 4>1C 70;56=> 2V4 V=482V4C0;L=>W ?5@5=>A8<>ABV.
=865==O @878:C @>728B:C V=AC;LBC C ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN V
3V?5@B@>DVTN ;V2>3> H;C=>G:0, I> 4>:C<5=B0;L=> ?V4B25@465=> 70 4>?><>3>N
0728G09 ?>G0B:>20 4>70 AB0=>28BL 50 <3 ;>70@B0=C (1 B01;5B:0 >@VAB8 50 <3) 1 @07 =0 4>1C.
0;56=> 2V4 73> B8A:C 4> ;V:C20==O A;V4 4>40B8 3V4@>E;>@BV0784 C =87L:V9 4>7V B0/01>
71V;LH8B8 4>7C >@VAB8 4> 100 <3 1 @07 =0 4>1C.
:@5
0AB>AC20==O ?0FVT=B0< 7V 7=865=8< >IT<>< F8@:C;NNG>W :@>2V
0FVT=B0< 7V 7=865=8< >IT<>< F8@:C;NNG>W :@>2V (=0?@8::04, C=0A;V4>: ;V:C20==O 28A>:8<8
4>70<8 4VC@5B8:V2) @>7?>G8=0B8 B5@0?VN =5>1EV4=> 7 4>78 25 <3 1 @07 =0 4>1C.
0AB>AC20==O ?0FVT=B0< V7 ?>@CH5==O< DC=:FVW =8@>: B0 ?0FVT=B0<, O:8< ?@>2>4OBL
A50=A8 35<>4V0;V7C
@8 ?@87=0G5==V >@VAB8 ?0FVT=B0< V7 ?>@CH5==O< DC=:FVW =8@>: B0 ?0FVT=B0<, O:8<
?@>2>4OBL A50=A8 35<>4V0;V7C, ?>G0B:>2C :>@5:FVN 4>78 ?@>2>48B8 =5 ?>B@V1=>.
0AB>AC20==O ?0FVT=B0< V7 ?>@CH5==O< DC=:FVW ?5GV=:8
;O ?0FVT=BV2 V7 ?>@CH5==O< DC=:FVW ?5GV=:8 2 0=0<=57V A;V4 @>73;O=CB8 ?8B0==O I>4>
?@87=0G5==O ?@5?0@0BC C <5=HV9 4>7V. 5<0T 4>A2V4C ;V:C20==O ?0FVT=BV2 V7 BO6:8<8
?>@CH5==O<8 DC=:FVW ?5GV=:8, B>70@B0= ?@>B8?>:070=89 FV9 3@C?V ?0FVT=BV2.
0AB>AC20==O 4VBO<
0=V I>4> 5D5:B82=>ABV B0 157?5:8 70AB>AC20==O ;>70@B0=C 4VBO< 2V:<< 6-18 @>:V2 4;O
;V:C20==O 0@B5@V0;L=>W 3V?5@B5=7VW >1<565=V. "0:>6 T<0;> 40=8E I>4> D0@<0:>:V=5B8:8 C
4VB59 7 0@B5@V0;L=>N 3V?5@B5=7VTN 2V:<< 2V4 1 20 :3 B0 <5=H5 50 :3, @5:><5=4>20=0 4>70
AB0=>28BL 25 <3 1 @07 =0 4>1C. # 28=OB:>28E 28?04:0E 4>7C <>6=0 71V;LH8B8 4> <0:A8<0;L=>W 50
<3 1 @07 =0 4>1C. >7C A;V4 :>@83C20B8 70;56=> 2V4 2?;82C =0 @V25=L 0@B5@V0;L=>3> B8A:C.
?0FVT=BV2 7 <0A>N BV;0 ?>=04 50 :3 70728G09 @07>20 4>70 AB0=>28BL 50 <3 1 @07 =0 4>1C. #
28=OB:>28E 28?04:0E 4>7C <>6=0 71V;LH8B8 4> <0:A8<0;L=>W 100 <3 1 @07 =0 4>1C. 0AB>AC20==O
4>7, I> ?5@528ICNBL 1,4 <3/:3 (01> 1V;LH5 100 <3) =0 4>1C, C 4VB59 =5 282G0;>AO.
>70@B0= =5 @5:><5=4>20=89 4;O 70AB>AC20==O 4VBO< 2V:<< 4> 6 @>:V2, >A:V;L:8 40=8E I>4>
70AB>AC20==O ?@5?0@0BC C FV9 3@C?V ?0FVT=BV2 =54>AB0B=L>.
@5?0@0B =5 @5:><5=4CTBLAO 4;O 70AB>AC20==O 4VBO< 7V H284:VABN ;;C1>G:>2>W
DV;LB@0FVW <
30 <:/E2/1,73 <2, >A:V;L:8 =5<0T 2V4?>2V4=8E 40=8E I>4> 70AB>AC20==O.
>70@B0= B0:>6 =5 @5:><5=4CTBLAO 4;O 70AB>AC20==O 4VBO< V7 ?>@CH5==O< DC=:FVW
?5GV=:8.

0AB>AC20==O ?0FVT=B0< ;VB=L>3> 2V:C
/: ?@028;>, =5<0T ?>B@518 C :>@83C20==V ?>G0B:>2>W 4>78 4;O ?0FVT=BV2 ;VB=L>3> 2V:C, E>G0
A;V4 2@0E>2C20B8 <>6;82VABL ?@87=0G5==O ?@5?0@0BC C ?>G0B:>2V9 4>7V 25 <3 ?0FVT=B0
< AB0@H5
75 @>:V2.

>1VG=V @50:FVW.
>1VG=>N @50:FVTN, ?@> O:C =09G0ABVH5 ?>2V4<<;O;>AO ?V4 G0A ;;V=VG=8E 4>A;V465==L, 1C;>
70?0<>@>G5==O.
@B5@V0;L=0 3V?5@B5=7VO.

I>:C =5@2>2>W A8AB5<8: 70?0<>@>G5==O, A>;;82VABL, 3>;>2=89 1V;L, 157A>==O,<O7>2V AC4><8.

I>:C A5@FO: 2V4GCBBO A5@F518BBO, AB5=>:0@4VO.

I>:C AC48==>W A8AB5<8: A8<0B8G=0 3V?>B5=7VO (>A>1;82> C ?0FVT=BV2 7 2=CB@VH=L>AC48==>N 453V4@0B0FVTN, =0?@8;;04 C ?0FVT=BV2 7 BO6:>N A5@F52>N =54>AB0B=VABN 01> ?@8 ;V:C20==V 4VC@5B8:0<8 C 28A>;8E 4>70E), 4>7>70;56=89 >@B>AB0B8G=89 5D5:B.

I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: 28A8?.

I>:C B@02=>3> B@0:BC: 014>@.

I>:C @5A?V@0B>@=>W A8AB5<8: :0H5;L, =568BL, A8=CA8B, D0@8=3VB, V=D5:FVO 25@E=VE 48E0;L=8E H;OEV2.

030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7VA?>A>I>< 70AB>AC20==O ?@5?0@0BC: 0AB5=VO, A;01:VABL, =01@O:8.

01>@0B>@=V ?>:07=8:8. @0B>@=8E ?>:07=8:V2 @V4:> 1C;8 ?>2O70=V V7 70AB>AC20==O< B01;5B>;>70@B0=C. V25=L " ?V428IC202AO @V4:> V 70728G09 =>@<0;V7C202AO ?VA;O ?@8?8=5==O 70AB>AC20==O ?@5?0@0BC. □V?5@:0;VT (@V25=L :0;VN C A8@>20BFV :@>2V > 5,5 <<>;L;) A?>AB5@V30;0AO C 1,5 % ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN. 0FVT=B8 7 3V?5@B@>DVTN ;V2>3> H;C=>G:0 A5@FO.

I>:C =5@2>2>W A8AB5<8: 70?0<>@>G5==O.

I>:C >@30=V2 A;CEC B0 ;01V@8=BC: 25@B83>.

030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7VA?>A>I>< 70AB>AC20==O ?@5?0@0BC: 0AB5=VO /A;01:VABL.

%@>=VG=0 A5@F520 =54>AB0B=VABL

I>:C =5@2>2>W A8AB5<8: 70?0<>@>G5==O, 3>;>2=89 1V;L, ?0@5AB57VO.

I>:C A5@FO: A8=>?5, DV1@8;OFVO ?5@54A5@4L, V=AC;LB.

I>:C AC48==>W A8AB5<8: 0@B5@V0;L=0 3V?>B5=7VO, 2;;NG0NG8 4>7>70;56=89 >@B>AB0B8G=89 5D5:B.

I>:C @5A?V@0B>@=>W A8AB5<8, >@30=V2 3@C4=>W ;:VB:8 B0 A5@54>ABV==O: 48A?=>5.

I>:C B@02=>3> B@0:BC: 4V0@5O, =C4>B0, 1;N20==O.

I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: :@>?82O=:0, A25@1V6, 28A8?.

I>:C =8@>: B0 A5G>282V4=8E H;OEV2: ?>@CH5==O DC=:FVW =8@>;, =8@>:20 =54>AB0B=VABL 030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7VA?>A>I>< 70AB>AC20==O ?@5?0@0BC: 0AB5=VO /A;01:VABL.

01>@0B>@=V ?>:07=8:8: 3V?5@:0;VT28=8 :@>2V, :@50B8=V=C C A8@>20BFV :@>2V B0 :0;VN C A8@>20BFV :@>2V.

@B5@V0;L=0 3V?5@B5=7VO V FC:@>289 4V015B B8?C , I> AC?@>2>46CTBLAO 70E2>@N20==O< =8@>:.

I>:C =5@2>2>W A8AB5<8: 70?0<>@>G5==O.

I>:C AC48==>W A8AB5<8: 0@B5@V0;L=0 3V?>B5=7VO.

030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7VA?>A>I>< 70AB>AC20==O ?@5?0@0BC: 0AB5=VO /A;01:VABL.

01>@0B>@=V ?>:07=8:8: 3V?>3;V:5

>40B:>2V ?>1VG=V @50:FVW.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 0=5

I>:C A5@FO: A8=>?5, ?0;L?VB0FVO.

I>:C AC48==>W A8AB5<8: >@B>AB0B8G=0 3V?>B5=7VO.

I>:C B@02=>3> B@0:BC: 4V0@5O.

I>:C A:5;5B=>-<O7>2>W A8AB5<8 B0 A?>;CG=>W B:0=8=8: 1V;L C A?8=V.

I>:C =8@>: B0 A5G>282V4=8E H;OEV2: V=D5:FVW A5G>282V4=8E H;OEV2.

030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7VA?>A>I>< 70AB>AC20==O ?@5?0@0BC: 3@8?>?>4V1=V A8<8.

01>@0B>@=V ?>:07=8:8: 3V?5@:0;VT28< 4V015B<< B8?C V =5D@>?0BVTN).

>AB<0@:5B8=3>25 A?>AB5@565==O.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 0=5<1>F8B>?5=VO.

I>:C >@30=V2 A;CEC B0 ;01V@8=BC: 472V= C 2CE0E.

I>:C VW A8AB5<8: @V4:> @50:FVW 3V?5@GCB;82>ABV (0=0DV;0:B8G=V @50:FVW, 0=3V>=52@>B8G=89 =01@O:, 2;:NG0NG8 =01@O: 3>@B0=V B0 3>;>A>2>W IV;8=8, I> ?@872>48BL 4> >1AB@C:FVW 48E0;L=8E H;OEV2 B0/01> =01@O:8 >1;8GGO, 3C1, 3;>B:8 V/01> O78:0); C 450:8E ?0FVT=BV2 2 0=0<=57V 1C2 0=3V>=52@>B8G=89 =01@O:, ?>2'O70=89 V7 70AB>AC20==O< V=H8E ?@5?0@0BV2, C B>@V2 \$; 20A:C;VB, 2;:NG0NG8 ?C@?C@C (5=;O9=- 5=>E0.

I>:C =5@2>2>W A8AB5<8:

I>:C @5A?V@0B>@=>W A8AB5<8, >@30=V2 3@C4=>W ;:VB:8 B0 A5@54>ABV==O: :0H5;L.

I>:C B@02=>3> B@0:BC: 4V0@5O, ?0=:@50B8B, 1;N20==O.

030;L=89 AB0= B0 ?>@CH5==O, ?>2O70=V 7V A?>A>1< 70AB>AC20==O ?@5?0@0BC: =574C65==O.

I>:C 35?0B>IV;V0@=>W A8AB5<8: 35?0B8B, ?>@CH5==O DC=:FVW ?5GV=:8.

I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: :@>?82O=:0, A25@1V6, 28A8?, D>B>GCB;82VABL, 5@8B@>45@

I>:C A:5;5B=>-<O7>2>W A8AB5<8 B0 A?>;CG=>W B:0=8=8: ;V7.

I>:C @5?@>4C:B82=>W A8AB5<8 V<>;>G=8E 70;>7: 5@5:B8;L=0 48ADC=:FVO/VB5=FVO.

I>:C =8@>: V A5G>282V4=8E H;OEV2: O: =0A;V4>: V=3V1C20==O @5=V=-0=3V>B5=78=-

0;L4>AB5@>=>2>W A8AB5<8 ?>2V4><;O;>AO ?@> 7:, 2;:NG0NG8 =8@:>2C =54>AB0B=VABL, C ?0FVT=BV2 3@C?8 @878:C; B0:V 72>W DC=:FVW <>6CBL 1CB8 >1>@>B=8<8 ?@8 ?@8?8=5==V B5@0?VW.

I>:C ?A8EV:8: 45?@5AVO.

01>@0B>@=V ?>:07=8:8: 3V?>=0B@VT

VB8

@>DV;L ?>1VG=8E @50:FV9 C 4VB59 ?>4V1=89 4> ?@>DV;N C 4>@>A;8E ?0FVT=BV2. 0=V AB>A>2=> ?>1VG=8E @50:FV9 C 4VB59 >1<565=V.

5@54>7C20==O.

!8<8

A=CNBL >1<565=V 40=V I>4> ?5@54>7C20==O ;>70@B0=> 2V4 ABC?5=O V=B>:A8:0FVW <>6CBL 7O2;OB8AO B0:V A8<8, O: 0@B5@V0;L=0 3V?>B5=7VO, B0EV:0@4VO, <>6;820 1@048:0@4VO.

V:C20==O

V:C20;L=V 70E>48 70;560BL 2V4 B@820;>ABV G0AC, I><8=C2 ?VA;O ?@89>ABV A8@8B5B=8< 70E>4>< <0T 1CB8 AB01V;V70FVO DC=:FVW A5@F52>-AC48==>W A8AB5<8. VA;O ?5@>@0;L=>3> ?5@54>7C20==O ?>:070=5 70AB>AC20==O 0:B82>20=>3> 2C3V;;O C 2V4?>2V4=V9 4>7V. 5:<5=4>20=8 <8 70E>40<8 T AB8<820==O H;C=:0. V7=VH5 A;V4 G0AB> :>=B@>;N20B8 >A=>2=V ?>:07=8:8 68BBT4VO;L=>ABV >@30=V7@83C20B8 ?@8 =5>1EV4=>ABV. >70@B0= B0 0:B82=V<5B01>;VB8 =5 2840;ONBLAO ?@8 ?@>2545==V 35<>4V0;V7C.

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

03VB=VABL

@5?0@0B ?@>B8?>:070=> 70AB>A>2C20B8 203VB=8< 01> 6V=:0<, O:V ?;0=CNBL 70203VB=VB8. /:I> ?V4 G0A ;V:C20==O ?@5?0@0B< ?V4B25@46CTBLAO 203VB=VABL, 9>3> 70AB>AC20==O =5>1EV4=> =5309=> ?@8?8=8B8 V 70

?V45;>3VG=V 40=V AB>A>2=> @878:C B5@0B>35==>3> 2?;82C 2=0A;V4>: 70AB>AC20==O

V=3V1VB>@V2 \$?@>BO3<< I B@8<5AB@C 203VB=>ABV =5 ?5@5:>=:82V, >4=0: =525;8:5

7@>AB0==O @878:C =5 28;:NG5=5. A:V;L:8 =5<0T :>=B@>;L>20=8E 5?V45;>3VG=8E 40=8E I>4>

@878:C 70AB>AC20==O 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C (), ?>4V1=V @878:8<>6CBL

VA=C20B8 V 4;O FL>3> ;:0AC ?@5?0@0BV2. 0 28=OB:< 28?04:V2, :>:8 ?@>4>265==O B5@0?VW

22060TBLAO =5>1EV4=8<, ?0FVT=B:0<, O:V ?;0=CNBL 203VB=VABL, A;V4 ?@87=0G8B8

0;LB5@=0B82=C 0=B83V?5@B5=782=C B5@0?VN 7V 2AB0=>2;5=8< ?@>DV;5< 157?5:8 I>4>

70AB>AC20==O C ?5@V>4 203VB=>ABV. /:I> 4V03=>AB>20=> 203VB=VABL, ;V:C20==O A;V4

=5309=> ?@8?8=8B8 V, O:I> =5>1EV4=>, A;V4 @>7?>G0B8 0;LB5@=0B82=5 ;V:C20==O. □V4<>, I>

70AB>AC20==O ?@>BO3<< II B0 III B@8<5AB@V2 203VB=>ABV 28;:8:0T ?>O2C D5B>B>:A8G=8E

O28I (7=865==O DC=:FVW =8@>:, >;V3>3V4@0<=V=>, 70B@8A8DV:0FVW :VAB>: G5@5?0) V

?@>O2V2 =5>=0B0;L=>W B>:A8G=>ABV (=8@:>20 =54>AB0B=VABL, 0@B5@V0;L=0 3V?>B5=7VO,

3V?5@0;VT

/:I> ?@>BO3<< B@8<5AB@C 203VB=>ABV 70AB>A>2C20;8AO , @5:><5=4>20=> ?@>25AB8
C;LB@072C:>25 >1AB565==O 4;O ?5@52V@:8 DC=:FVW =8@>: V AB0=C :VAB>: G5@5?0
!B0= =>2>=0@>465=8E, <0B5@V O:8E 70AB>A>2C20;8 , A;V4 G0AB> ?5@52V@OB8 AB>A>2=>
@>728B:C 0@B5@V0;L=>W 3V?>B5=7VW.

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

'5@57 2V4ACB=VABL 1C4L-O:>W V=D>@<0FVW I>4> 70AB>AC20==O ;>70@B0=C C ?5@V>4
3>4C20==O 3@C44N ?@89<< ;>70@B0=C =5 @5:><5=4CTBLAO. 060=> 70AB>A>2C20B8
0;LB5@=0B82=V ?@5?0@0B8 7 :@0I8<8 2AB0=>2;5=8<8 ?@>DV;O<8 157?5:8 C ?5@V>4 3>4C20==O
3@C44N, >A>1;82> ?@8 3>4C20==V =>2>=0@>465=8E 01> =54>=>H5=8E =5<>2;OB.

VB8.

>70@B0= =5 @5:><5=4CTBLAO 4;O 70AB>AC20==O 4VBO< 2V:> 4> 6 @>:V2, >A:V;L:8 I>4> FVTW
3@C?8 ?0FVT=BV2 40=V T >1<565=8<8.

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

=3V>=52@>B8G=89 =01@O:

>6;825 28=8:=5==O 0=3V>=52@>B8G=>3> =01@O:C. !;V4 G0AB> :=B@>;N20B8 AB0= ?0FVT=BV2 7
0=3V>=52@>B8G=8< =01@O:>< (=01@O:8 >1;8GGO, 3C1, 3>@;0 B0/01> O78:0) 2 0=0<=57V.

@B5@V0;L=0 3V?>B5=7VO V 2>4=>-5;5:B@>;VB=89 48A10;0=A

!8<0B8G=0 0@B5@V0;L=0 3V?>B5=7VO, >A>1;82> ?VA;O 70AB>AC20==O ?5@H>W 4>78 ?@5?0@0BC
01> ?VA;O ?V428I5==O 4>78, <65 28=8:0B8 C ?0FVT=BV2 7V 7=865=8< 2=CB@VH=L>AC48==8< >1T
<< 01> 45DVf8B>< =0B@VN, A?@8G8=5=8<8 70AB>AC20==O< A8;L=8E 4VC@5B8:V2, 4VTB8G=8<
>1<565==O< A?>6820==O A>;V, 4V0@5TN 01> 1;N20==CB@51CNBL :>@5:FVW ?5@54 ?>G0B:>
>V:C20==O >@VAB>N[®] 01> 7=865==O ?>G0B:>2>W 4>78 ?@5?0@0BC. "0:V 6 @5:><5=40FVW
AB>ACNBLAO 4VB59 2V:> 2V4 6 4> 18 @>:V2.

;5:B@>;VB=89 48A10;0=A

;5:B@>;VB=89 48A10;0=A G0AB> A?>AB5@V30TBLAO C ?0FVT=BV2 V7 ?>@CH5==O< DC=:FVW
=8@>: (7 FC:@>28< 4V015B>< 01> 157 =L>3>), I> A;V4 1@0B8 4> C2038. V4 G0A ;:V=VG=>3>
4>A;V465==O 70 CG0ABN E2>@8E =0 FC:@>289 4V015B II B8?C B0 7 =5D@>?0BVTN G0AB>B0
28=8:=5==O 3V?5@:0;VTN ?@8 ;V:C20==V ;>70@B0=>?>@V2=O=> 7 B0:>N C 3@C?V ?;0F51>. ">
?5@52V@OB8 :=F5=B@0FVN :0;VN C ?;072V V ?>:07=8:8 ;:V@5=AC :@50B8=V=C, >A>1;82> C
?0FVT=BV2 V7 A5@F52>N =54>AB0B=VABN V ;:V@5=A< :@50B8=V=C 30-50 <:/E2.

5 @5:><5=4>20=5 >4=>G0A=5 70AB>AC20==O ;>70@B0=C V :0;V9715@V30NG8E 4VC@5B8:V2,
4>102>;, I> ;V, I>

>@CH5==O DC=:FVW ?5GV=:8

h@C=BCNG8AL =0 D0@<0:>:V=5B8G=8E 40=8E, I> 2:07CNBL =0 VAB>B=5 ?V428I5==O
:=F5=B@0FVW ;>70@B0=C C ?;072V E2>@8E =0 F8@>7 ?5GV=:8, A;V4 @>73;O=CB8 ?8B0==O ?@>
7=865==O 4>78 4;O ?0FVT=BV2 V7 =0O2=VABN 2 0=0<=57V ?>@CH5=L DC=:FVW ?5GV=:8. 5<0T
4>A2V4C B5@0?52B8G=>3> 70AB>AC20==O ;>70@B0=C ?0FVT=B0< V7 BO6:8<8 ?>@CH5==O<8
DC=:FVW ?5GV=:8, B>70@B0= =5 <>6=0 ?@89<0B8 B0:8< ?0FVT=B0
>70@B0= =5 @5:><5=4>20=89 4;O 70AB>AC20==O 4VBO< V7 ?>@CH5==O<8 DC=:FVW ?5GV=:8.
>@CH5==O DC=:FVW =8@>:

>2V4><;O;>AO ?@> 28=8:=5==O 7.;, 2;;NG0NG8 =8@:>2C =54>AB0B=VABL, I> ?>2O7C20;8 7
?@83=VG5==O< @5=V=-0=3V>B5=78=>2>W A8AB5<8 (>A>1;82> C ?0FVT=BV2 V7 70;56=VABN
DC=:FVW =8@>: 2V4 A8AB5<8 @5=V=-0=3V>B5=78=-0;L4>AB5@>=, B>1B> ?0FVT=B8 7 BO6:>N
A5@F52>N =54>AB0B=>ABN 01> 7 C65 VA=CNG8<8 ?>@CH5==O<8 DC=:FVW =8@>:).

@5?0@0B8, I> 2?;820NBL =0 @5=V=-0=3V>B5=78=-0;L4>AB5@>=>2C A8AB5: <>6CBL 1CB8
>1>@>B=8<8 ?VA;O ?@8?8=5==O B5@0?VW. >70@B0= A;V4 7 >15@56=VABN 70AB>A>2C20B8
?0FVT=B0< V7 42>1VG=8< AB5=>7< =8@:>28E 0@B5@V9 01> AB5=>7< 0@B5@VW T48=>W =8@:8.
0AB>AC20==O 4VBO< V7 ?>@CH5==O<8 DC=:FVW =8@>:

>70@B0= =5 @5:><5=4>20=89 4;O 70AB>AC20==O 4VBO< 7V H284:VABN ;:C1>G:>2>W
DV;LB@0FVW < 30 <:/E2/1,73 <2, >A:V;L:8 =5<0T 2V4?>2V4=8E 40=8E I>4> 70AB>AC20==O.

@>B03<< ?5@V>4C 70AB>AC20==O ;>70@B0=C A;V4 @53C;O@=> ?5@52V@OB8 DC=:FVN =8@>.;
>A;V;L:8 <>6;825 WW ?>3V@H0==O. A>1;82> F5 AB>ACTBLAO A8BC0FV9, :>8 ;>70@B0=
70AB>A>2CNBL ?@8 =0O2=>ABV V=H8E ?0B0;>3VG=8E AB0=V2 (30@OG:0, 453V4@0B0FVO), O:V
<>6CBL 2?;820B8 =0 =8@:>2C DC=:FVN.
4=>G0A=5 70AB>AC20==O ;>70@B0=C B0 V=3V1VB>@V2 \$?>3V@HCT DC=:FVN =8@>.; B>
<1V=0FVO =5 @5:><5=4>20=0.
"@0=A?;0=B0FVO =8@:8
5<0T 4>A2V4C I>4> 157?5:8 70AB>AC20==O ?@5?0@0BC ?0FVT=B0<, O:8< =5I>402=> ?@>2545=>
B@0=A?;0=B0FVN =8@:8.
5@28==89 3V?5@0;L4>AB5@>=V7<
?0FVT=BV2 V7 ?5@28==8< 3V?5@0;L4>AB5@>=V7<<<, O: ?@028;>, =5 A?>AB5@V30TBLAO 5D5:BC
?@8 70AB>AC20==V 0=B83V?5@B5=782=8E ?@5?0@0BV2, I> 4VNBL I;OE<< ?@83=VG5==O @5=V=-
0=3V>B5=78=>2>W A8AB5<8. ">@VAB0 =5 @5:><5=4>20=0 4;O FVTW 3@C?8 ?0FVT=BV2.
0E2>@N20==O :>@>=0@=8E 0@B5@V9 B0 F5@51@>20A:C;O@=V 70E2>@N20==O
/: V ?@8 70AB>AC20==V V=H8E 0=B83V?5@B5=782=8E ?@5?0@0BV2, =043> B8A:C C ?0FVT=BV2 7
VH5:0@40 01> V=AC;LBC.
!5@F520 =54>AB0B=VABL
/: V ?@8 70AB>AC20==V V=H8E ?@5?0@0BV2, I> 2?;820NBL =0 @5=V=-0=3V>B5=78=-
0;L4>AB5@>=>2C A8AB5N =54>AB0B=VABN 7 ?>@CH5==O< DC=:FVW =8@>: 01> 157 =L>3> VA=CT
@878: @>728B:C B06:>W 0@B5@V0;L=>W 3V?>B5=7VW V (G0AB> 3>AB@>3>) ?>@CH5==O
DC=:FVW =8@>:.
5<0T 4>AB0B=L>3> B5@0?52B8G=>3> 4>A2V4C 70AB>AC20==O ;>70@B0=C ?0FVT=B0< V7
A5@F52>N =54>AB0B=VABN V AC?CB=V< B06:8< ?>@CH5==O< DC=:FVW =8@>.; ?0FVT=B0< V7
B06:>N A5@F52>N =54>AB0B=VABN (:0A IV 70 :;0A8DV:0FVTN NYHA), 0 B0:>6 ?0FVT=B0< V7
A5@F52>N =54>AB0B=VABN V A8<0B8G=>N, =5157?5G=>N 4;O 68BBO A5@F52>N 0@8B70@B0=
A;V4 70AB>A>2C20B8 7 >15@56=VABN B0:V9 3@C?V ?0FVT=BV2. !;V4 7 >15@56=VABN >4=>G0A=>
70AB>A>2C20B8 :><1V=0FVN ;>70@B0=C 7 ?-1;>:0B>@0<8.
!B5=>7 0>@B0;L=>3> V 3> :;0?0=V2, >1AB@C:B82=0 3V?5@B@>DVG=0 :0@4V>?0BV0
/: V ?@8 70AB>AC20==V V=H8E 207>48;0B0B>@V2, 7 >A>1;82>N >15@56=VABN ?@87=0G0NBL
?@5?0@0B ?0FVT=B0< 7V AB5=>7<< 0>@B0;L=>3> 01> 3> :;0?0=0 01> >1AB@C:B82=>N
3V?5@B@>DVG=>N :0@4V>?0BVTN.
03VB=VABL
0AB>AC20==O 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C =5 A;V4 @>7?>G8=0B8 ?V4 G0A
203VB=>ABV. 0 28=OB:>< 28?04:V2, :>8 ?@>4>265==O B5@0?VW 22060TBLAO =5>1EV4=8<,
?0FVT=B:0<, O:V ?;0=CNBL 203VB=VABL, A;V4 ?@87=0G8B8 0;LB5@=0B82=C 0=B83V?5@B5=782=C
B5@0?VN V7 2AB0=>2;5=8< ?@>DV;5< 157?5:8 I>4> 70AB>AC20==O C ?5@V>4 203VB=>ABV. !:I>
4V03=>AB>20=> 203VB=VABL, ;V:C20==O A;V4 =5309=> ?@8?8=8B8 V, O:I> =5>1EV4=>, A;V4
@>7?>G0B8 0;LB5@=0B82=5 ;V:C20==O.
=HV ?>?5@5465==O V 70AB5@565==O
/: 2AB0=>2;5=> AB>A>2=> V=3V1VB>@V2 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC, ;>70@B0=
B0 V=HV 0=B03>=VAB8 0=3V>B5=78=C<5=H 5D5:B82=V 4;O 7=865==O 0@B5@V0;L=>3> B8A:C C
?0FVT=BV2 =53@>W4=>W @0A8, =V6 2 V=H8E ?0FVT=BV2, <>6;82>, G5@57 =87L:C 0:B82=VABL
@5=V=C C 3@C?V =53@>W4=8E ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN.
A>1;820 V=D>@<0FVO ?@> 45O:V 7 4>?>28=
>@VAB07C. 0FVT=B0< V7 @V4:VA=8<8 A?04:>28<8 D>@<0<8 =5?5@5=>A8<>ABV 30;0:B>78,
45DVF8B<< ;0:B078 0?0 01> ?>@CH5==O< 2A<>:BC20==O 3;N:>78-30;0:B>78 =5 A;V4
70AB>A>2C20B8 F59 ?@5?0@0B.
>42V9=0 I;>:040 @5=V=-0=3V>B5=78=-0;L4>AB5@>=>2>W A8AB5<8 (!)
@8 AC?CB=L>AC20==V 0;VA:V@5=C B0 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C 01>
V=3V1VB>@V2 \$?V428ICTBLAO @878: 0@B5@V0;L=>W 3V?>B5=7VW, 3V?5@:0;VT:, 2;NG0NG8
3>AB@C =8@:>2C =54>AB0B=VABL. # 7207:C 7 ?>42V9=>N 1;>:04>N @5=V=-0=3V>B5=78=-
0;L4>AB5@>=>2>W A8AB5<8 (!) AC?CB=T 70AB>AC20==O 0;VA:V@5=C B0 0=B03>=VABV2
@5F5?B>@V2 0=3V>B5=78=C 01> V=3V1VB>@V2 \$ =5 @5:><5=4CTBLAO (482. @>74V; «□70T<>4V0
7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). # 28?04:C :@09=L>W =5>1EV4=>ABV
?>42V9=>W 1;>:048 ! A;V4 @5B5;L=> ?5@52V@OB8 DC=:FVN =8@>.; @V25=L 5;5:B@>;VBV2 C

:@>2V B0 0@B5@V0;L=89 B8A.: 5 A;V4 >4=>G0A=> 70AB>AC20B8 0=B03>=VAB8 @5F5?B>@V2
0=3V>B5=78=C B0 V=3V1VB>@8 \$?0FVT=B0< 7 FC:@>28< 4V015B>

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.

5 ?@>2>48;8AO 4>A;V465==O I>4> 2?;82C ?@5?0@0BC =0 740B=VABL C?@02;OB8 02B>B@0=A?>@B>
< B0 V=H8<8 <5E0=V7<0<8. 4=0: A;V4 ?0<OB0B8 ?@> <>6;82VABL @>728B:C B0:8E ?>1VG=8E
@50:FV9, O: 70?0<>@>G5==O B0 A=>;82VABL, >A>1;82> =0 ?>G0B:C ;V:C20==O B0 ?@8 ?V428I5==V
4>78 ?@5?0@0BC.

70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

=HV 0=B83V?5@B5=782=V ?@5?0@0B8 <>6CBL ?>A8;N20B8 3V?>B5=782=89 5D5:B ;>70@B0=C. >
V=H8E ?@5?0@0BV2, I> <>6CBL 28;;8:0B8 0@B5@V0;L=C 3V?>B5=7VN, =0;560BL B@8F8;;VG=V
0=B845?@5A0=B8, 0=B8?A8E>B8G=V 70A>18, 10;;>D5=, 0AB8=. A=>2=8< 01> ?>1VG=8< 5D5:B><
>4=>G0A=>3> 70AB>AC20==O F8E ?@5?0@0BV2 V7 3V?>B5=782=8<8 70A>10<8 <>65 1CB8
71V;LH5==O @878:C 28=8:=5==O 0@B5@V0;L=>W 3V?>B5=7VW. >70@B0=<5B01>;V7CTBLAO
?5@5206=> 70 CG0ABN A8AB5<8 F8B>E@>@5==O< 0:B82=>3> <5B01>;VBC :0@1>:A8;L=>W :8A;>B8.
E>4V ;;V=VG=8E 4>A;V465==L 1C;> 2AB0=>2;5=>, I> D;C:>=07>; (V=3V1VB>@ CYP2C9) 7=86CT
5:A?>78FVN 0:B82=>3> <5B01>;VBC ?@81;87=> =0 50 %. AB0=>2;5=>, I> >4=>G0A=5 70AB>AC20==O
>70@B0=C B0 @8D0@0 D5@<5=BV2 <5B01>;V748BL 4> 7=865==O =0 40 % :>=F5=B@0FVW
0:B82=>3> <5B01>;VBC C ?;072V. ;V=VG=5 7=0G5==O FL>3> 5D5:BC =52V4<5. 5<0T 2V4ABV 2
5:A?>78FVW ?@8 >4=>G0A=>AC20==V ;>70@B0=C B0 D;C20AB0B8=C (A;01:>3> V=3V1VB>@C
CYP2C9). "0: A0<>, O: V ?@8 70AB>AC20==V V=H8E ?@5?0@0BV2, O:V 1;>;:CNBL 0=3V>B5=78= 01>
9>3> 5D5:B8, >4=>G0A=5 70AB>AC20==O ?@5?0@0BV2, I> 70B@8@30=V7=>;0:B>=C, B@V0@84C)
01> <>6CBL ?V428IC20B8 @V2=V :0;VN (B0:8E O: 35?0@8=), 01> 4>102>.; I> 70;V 7 :0;VT< <>65
?@8725AB8 4> ?V428I5==O 220BFV :@>2V. 4=>G0A=5 70AB>AC20==O B0:8E 70A>1V2 =5 @5:>
<5=4>20=5. @> >1>@>B=5 ?V428I5==O :>=F5=B@0FVW ;VBN C A8@>20BFV :@>2V B0 28=8:=5==O
B>:A8G=8E ?@>O2V2 ?>2V4<;O;>AO ?@8 >4=>G0A=>AC20==V ;VBN 7 V=3V1VB>@0<8 \$. "0:>6
4C65 @V4:> ?>2V4<;O;>AO ?@> B0:V ?@>O28 ?@8 70AB>AC20==V 0=B03>=VABV2 @5F5?B>@V2
0=3V>B5=78=C . 4=>G0A=5 ;V:C20==O ?@5?0@0B0<8 ;VBN B0 ;>70@B0=< A;V4 ?@>2>48B8 7
>15@56=VABN. /:I> 70AB>AC20==O B0:>W :<1V=0FVW 22060TBLAO =5>1EV4=8<, @5:><5=4>20=>
?5@52V@OB8 @V25=L ;VBN 2 A8@>20BFV :@>2V ?@>B03< :<1V=>20=>3> ;V:C20==O.
@8 >4=>G0A=>AC20==V 0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C V =5AB5@>W4=8E
?@>B870?0;L=8E ?@5?0@0BV2 (=0?@8;;04 A5;5:B82=8E V=3V1VB>@V2 F8;;>:A835=078-2
(?A0;VF8;>2>W :8A;>B8 C 4>70E, I> G8=OBL ?@>B870?0;L=C 4VN, =5A5;5:B82=8E) <>65
?>A;01;N20B8AO 0=B83V?5@B5=782=89 5D5:B. 4=>G0A=5 70AB>AC20==O 0=B03>=VABV2
0=3V>B5=78=C 01> 4VC@5B8:V2 V7 <>65 ?@872>48B8 4> ?V428I5==O @878:C ?>3V@H0==O
DC=:FVW =8@>.; 2;;NG0NG8 <>6;8289 @>728B>: 3>AB@>W =8@>:2>W =54>AB0B=>ABV, 0 B0:>6 4>
?V428I5==O @V2=O :0;VN C A8@>20BFV :@>2V, >A>1;82> C ?0FVT=V2 7 VA=CNG8 ?>@CH5==O<
DC=:FVW =8@>:. "0:C :<1V=0FVN A;V4 ?@87=0G0B8 7 >15@56=VABN, >A>1;82> ?0FVT=B0<
>VB=L>3> 2V:C. 0FVT=B0< A;V4 ?@>2>48B8 2V4?>2V4=C 453V4@0B0FVN, B0:>6 A;V4 @>73;O=CB8
?8B0==O I>4> <=>VB>@8=3C DC=:FVW =8@>: ?VA;O ?>G0B:C >4=>G0A=>3> 70AB>AC20==O
?@5?0@0BV2, 0 B0:>6 ?5@V>48G=> 2?@>4>26 ;V:C20==O.
>A;V465==O ?>:070;8, I> 2=0A;V4>: ?>42V9=>W 1;>;:048 ! ?@8 AC?CB=L>AC20==V V=3V1VB>@V2 \$,
0=B03>=VABV2 @5F5?B>@V2 0=3V>B5=78=C 01> 0;VA:V@5=C ?V428ICTBLAO @878: ?>1VG=8E
@50:FV9 B0:8E O:, 0@B5@V0;L=0 3V?>B5=7VO, 3V?5@:0;VT.; 2;;NG0NG8 3>AB@C =8@>:2C
=54>AB0B=VABL ?>@V2=O=> V7 70AB>AC20==O< >4=>3> 035=B0 @5=V=-0=3V>B5=78=-
0;L4>AB5@>=>2>W A8AB5<8 (482. @>74V;8 «@>B8?>:070==O», «A>1;82>ABV 70AB>AC20==O».

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

\$0@<0:>48=0

>70@B0= F5 A8=B5B8G=89 0=B03>=VAB @5F5?B>@V2 0=3V>B5=78=C (B8?C ") 4;O ?5@>@0;L=>3>
70AB>AC20==O. =3V>B5=78= ?>BC6=89 207>:>=AB@8:B>@ T 0:B82=8< 3>@<>=< @5=V=-
0=3V>B5=78=>2>W A8AB5<8 V >4=8< 7 =09206;82VH8E D0:B>@V2 ?0B>DV7V>;>3VW

0@B5@V0;L=>W 3V?5@B5=7VW. =3V>B5=78= II 72O7CTBLAO 7 @5F5?B>@< AT₁, O:89 E B:0=8=0E (=0?@8::04 C 3;04:8E <O70E AC48=, =04=8@:>28E 70;>70E, =8@:0E V A5@FV), 287=0G0NG8 =87:C 206;828E 1V>;>3VG=8E 5D5:BV2, C B>:=AB@8:FVN V 72V;L=5==O 0;L4>AB5@>=C. =3V>B5=78= B0:>6 AB8;VD5@0FVN ::VB8= 3;04:8E <O7V2.

>70@B0= A5;5:B82=> 72O7CTBLAO 7 @5F5?B>@< "1. C<>20E *Vn vitro* B0 *in vivo* ;>70@B0= B0 9>3> D0@<0:>;>3VG=> 0:B82=89 <5B01>;VB :0@1>:A8;L=0 :8A;>B0 (E-3174) 1;>:CNBL CAV DV7V>;>3VG=> 203>B5=78=C , =570;56=> 2V4 465@5;0 01> H;OEC A8=B57C.

>70@B0= =5 72O7CTBLAO V =5 1;>:CT V=HV @5F5?B>@8 3>@<=V2 01> V>==V :0=0;8, 206;82V 4;O A5@F52>-AC48==>W @53C;OFVW. >70@B0= =5 ?@83=VGCT \$ (:V=07C) D5@<5=B, O:89 A?@8OT @>7?04C 1@048:V=V=C. =0A;V4>: FL>3> =5 2V41C20TBLAO ?>A8;5==O =51060=8E 5D5:BV2, >?>A5@54:>20=8E 1@048:V=V=>

V4 G0A 70AB>AC20==O ;>70@B0=C CAC=5==O =530B82=>W >1>@>B=>W @50:FVW 0=3V>B5=78=C =0 A5:@5FVN @5=V=C ?@872>48BL 4> ?V428I5==O 0:B82=>ABV @5=V=C C ?;072V (). "0:5 ?V428I5==O ?@872>48BL 4> 7@>AB0==O :>=F5=B@0FVW 0=3V>B5=78=C C ?;072V. %>G0 2V41C20TBLAO B0:5 7@>AB0==O, 0=B83V?5@B5=782=0 0:B82=VABL V AC?@5AVO :>=F5=B@0FVW 0;L4>AB5@>=C C ?;072V 715@V30NBLAO, I> A2V4G8BL ?@> 5D5:B82=C 1;>:04C @5F5?B>@V2 0=3V>B5=78=C . VA;O 2V4 ;V:C20==O ;>70@B0=< 0:B82=VABL @5=V=C C ?;072V V ?>:07=8:8 @V2=V2 0=3V>B5=78=C ?@>B03>< 3 4=V2 ?>25@B0NBLAO 4> ?>G0B:>28E 7=0G5=L. /: ;>70@B0=, B0: V 9>3> >A=>2=89 <5B01>;VB <0NBL 28IC A?>@V4=5=VABL 7 "1-@5F5?B>@0<8, =V6 7 "2-@5F5?B>@0<8. :B82=89 <5B01>;VB C 10-40 @07V2 0:B82=VH89, =V6 ;>70@B0=.

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

IA>@FVO

VA;O ?5@>@0;L=>3> ?@89>70@B0= 4>1@5 2A<>:BCTBLAO V ?V4;O30T <5B01>;V73> ?@>E>465==O 7 D>@ >7?>4V;

>=04 99 % ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC 72O7CNBLAO 7 ?@>B5W=0<8 ?;07<8 :@>2V, ?5@54CAV< 7 0;L1C34 ;.

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

@81;87=> 14 % ;>70@B0=C ?@8 2=CB@VH=L>25==> ?5@>@0;L=>AC20==V ?5@5B2>@NTBLAO =0 0:B82=89 <5B01>;VB. VA;O 2=CB@VH=L>25==>3> V ?5@>@0;L=>3> 70AB>AC20==O ;>70@B0=C :0;VN, 3> 14!, @04V>0:B82=VABL C F8@:C;NNGV9 ?;072V, O: ?@028;>, E0@0:B5@87CTBLAO ;>70@B0=< B0 9>3> <5B01>;VB> :@V< 0:B82=>3> <5B01>;VBC, CB2>@NNBLAO V =50:B82=V <5B01>;VB8. 82545==O ;07<>289 ;;V@5=A ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC AB0=>28BL 600<;E2 V 50 <;E2 2V4?>2V4=>. 8@:>289 ;;V@5=A ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC AB0=>28BL ?@81;87=> 74 <;E2 V 26 <;E2 2V4?>2V4=>. >;8 ;>70@B0= 70AB>A>2CNBL ?5@>@0;L=>, ?@81;87=> 4 % 4>78 284V;OTBLAO C =57 6 % 4>78 284V;OTBLAO V7 A5G5N C 283;O4V 0:B82=>3> <5B01>;VBC. \$0@ <0:>:V=5B8G=V 2;0AB82>ABV ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC ;V=V9=V ?@8 ?5@>@0;L=8E 4>70E ;>70@B0=C :0;VN 4> 200 <3. VA;O ?5@>@0;L=>3> 70AB>AC20==O :>=F5=B@0FVW C ?;072V ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC 7<5=HCNBLAO ?>;V5:A?>=5=V9=> 7 :V=F528< ?5@V>4<=0?V2282545==O ?@81;87=> 2 3>48=8 V 6-9 3>48= 2V4?>2V4=>. @8 4>7V 100 <3, 70AB>A>20=V9 1 @07 =0 4>1C, ;>70@B0= V 9>3> 0:B82=89 <5B01>;VB =5 =0:>?8GCNBLAO C ?;072V C 7=0G=V9 :V;L:>ABV. >70@B0= B0 9>3> <5B01>;VB8 282>4OBLAO O: V7 6>2GN, B0: V 7 A5G5N. VA;O ?5@>@0;L=>3> 70AB>AC20==O/2=CB@VH=L>25==>3> 22545==O 14!-3> ;>70@B0=C ?@81;87=> 35 %/43 % @04V>0:B82=> 3> ?@5?0@0BC 1C;> 28O2;5=> C A5GV V 58 %/50 % C :0;V. :@5 >=F5=B@0FVW ;>70@B0=C B0 9>3> 0:B82=>3> <5B01>;VBC C ?;072V ?0FVT=BV2 ;VB=L>3> 2V:C 7 0@B5@V0;L=>N 3V?5@B5=7VTN 7=0GCI> =5 2V4@V7=ONBLAO 2V4 40=8E ?>:07=8:V2 C <>;>48E ?0FVT=BV2 7 0@B5@V0;L=>N 3V?5@B5=7VTN. >=F5=B@0FVW ;>70@B0=C C ?;072V 1C;8 C 2 @078 28IV C 6V=>: 7 0@B5@V0;L=>N 3V?5@B5=7VN ?>@V2=O=> 7 G>;>2V:0<8, B>4V O: :>=F5=B@0FVW 0:B82=>3> <5B01>;VBC C ?;072V C G>;>2V:V2 V 6V=>: ACBBT2> =5 2V4@V7=O;8AO.

@8 ?@89> ?0FVT=B0<8 7 ;53:8< B0 ?>2V 28O2;O;8AO 2V4?>2V4=> C 5 B0 1,7 @070 28I8<8, =V6 C
<>;>48E G>;>2V:V2-4>1@>2>;LFV2.
>=F5=B@0FVW ;>70@B0=C C ?;072V C ?0FVT=BV2 V7 ;;V@5=A<< :@50B8=V=C 28I5 10 <;E2 =5
2V4@V7=O;8AO 2V4 B0:8E 2 >AV1 V7 =57N DC=:FVTN =8@>:. @8 ?>@V2=O==V ?;>IV ?V4 :@82>N
<<:=F5=B@0FVO-G0A» (AUC) C ?0FVT=BV2 V7 =>@<0;L=>N DC=:FVTN =8@>: AUC ;>70@B0=C,
28O28;0AO ?@81;87=> C 2 @078 1V;LH>N =V6 C ?0FVT=BV2, O:V ?5@51C20NBL =0 35<>4V0;V7V.
;07<>2V :=F5=B@0FVW 0:B82=>3> <5B01>;VBC =5 7@CH5==O< DC=:FVW =8@>: 01> E2>@8E, O:V
?5@51C20NBL =0 35<>4V0;V7V.

>70@B0= V 9>3> 0:B82=89 <5B01>;VB =5 <>6CBL 1CB8 282545=V 70 4>?<>3>N 35<>4V0;V7C.

\$0@<0>:V=5B8:0 C 4VB59

\$0@<0>:V=5B8:0 ;>70@B0=C 282G0;0AO 70 CG0ABN 50 4VB59 7 0@B5@V0;L=>N 3V?5@B5=7VTN
2V:<> 2V4 1 16 @>:V2 ?VA;O ?5@>@0;L=>3> 70AB>AC20==O 1 @07 =0 4>1C 2 4>70E 2V4 0,54 4> 0,77
<3/:3 (A5@54=V 4>78).

57C;LB0B8 ?>:070;8, I> 0:B82=89 <5B01>;VB ;>70@B0=C CB2>@NTBLAO C ?0FVT=BV2 CAVE

2V:>28E 3@C?. 57C;LB0B8 2:07CNBL =0 ?@81;87=> 0=0;>3VG=V ?>:07=8:8 D0@<0>:V=5B8:8

;>70@B0=C ?VA;O ?5@>@0;L=>3> 70AB>AC20==O C =>2>=0@>465=8E V 4VB59 4>H:V;L=>3> V
H:V;L=>3> 2V:C.

\$0@<0>:V=5B8G=V ?>:07=8:8 <5B01>;VBC 2V4@V7=O;8AO 1V;LH5 70;56=> 2V4 2V:>2>W 3@C?8. @8

?>@V2=O==V 4VB59 4>H:V;L=>3> 2V:C V ?V4;VB:V2 B0:V 2V4ABV 1C;8 AB0B8AB8G=> 7=0GCI8<8.

:A?>78FVO C =>2>=0@>465=8E V 4VB59 2V:<> 4> 2 @>:V2 1C;0 ?>@V2=O=> 28A>:>N.

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

A=>2=V DV78:>-EVABV: B01;5B:8 ?> 12,5 <3: 6>2BV >20;L=V, 45I> 42>>?C;;V B01;5B:8, 2:@8BV
?;V2:>2>N >1>;>=:>N;

B01;5B:8 ?> 25 <3: 6>2BV, >20;L=V, 45I>42>>?C;;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 7 @8A:>N
7 >4=>3> 1>:C;

B01;5B:8 ?> 50 <3: 1V;V, :@C3;V, 45I> 42>>?C;;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N, 7V A:>H5=8
<8 :@0O<8 B0 @8A:>N 7 >4=>3> 1>:C;

B01;5B:8 ?> 100 <3: 1V;V, >20;L=V, 45I> 42>>?C;;V B01;5B:8, 2:@8BV ?;V2:>2>N >1>;>=:>N.

"5@ABV. 5 @>:V2.

#<>28 715@V30==O.

15@V30B8 ?@8 B5C. 15@V30B8 C =54>ABC?=>

#?0:>2:0. 10 B01;5B>: C 1;VAB5@V; ?> 3 01> ?> 6, 01> ?> 9 1;VAB5@V2 C :0@B>==V9 :>@>1FV;

14 B01;5B>: C 1;VAB5@V; ?> 1 01> ?> 2, 01> ?> 4, 01> ?> 6, 01> ?> 7 1;VAB5@V2 C :0@B>==V9

:>@>1FV.

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

8@>1=8:.

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

KRKA, d.d., Novo mesto, Slovenia.

"\$0@

TAD Pharma GmbH, Germany.

VAF57=0E>465==O.

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

Smarjeska cesta 6, 8501 Novo mesto, Slovenia.

-27472 C:AE025=, %09=F->E<0==-(B@0AA5 5, V<5GG8=0/

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