!" #&/

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

"

!:;04:

4VNG0 @5G>28=0: 1 B01;5B:0 B025@@8=C 3V4@>E;>@@@84C C ?5@5@@@0EC20==V =0 100 %
@5G>28=C 40 <3;
4>?>28=8: :@>E<0;L :0@?>?;O=89; :0:B>70, <>=>3V4@@@0B; ?>2V4>=; :0;LFVN AB50@@@0B.

V:0@AL:0 D>@@<0. "01;5B:8.

A=>2=V DV78:>-EVABV: B01;5B:8 A2VB;>-6>2B>3>, A2VB;>-6>2B>3> 7 75;5=C20B8< 2V4BV=:><,
6>2B>3> 01> 6>2B>3> 7 75;5=C20B8< 2V4BV=< :>;L@@C :@C3;>W D>@@<8 7 ?;>A:>N ?>25@E=5N,
7 D0A:>N. 0 ?>25@E=V B01;5B>: <>6;820 <0@@2VABL.

$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, O:V 70AB>A>2CNBLAO ?@8 DC=:FV>=0;L=8E H;C=:>2>-
:8H:>28E @>7;040E. **>4 AT%** 03D02.

$0@<0:>:>;>3VG=V 2;0AB82>ABV
$0@<0:>:>48=0
@>B025@@8= ?>EV4=5 V7>EV=>;V=C, O:89 28O2;OT A?07<>;5@@8G=C 4VN =0 3;04:C <
?@83=VG5==O 4VW D5@@<5=BC D>AD>4V5AB5@070 IV ($IV), I> A?@8G8=OT 71V;LH5==O
:>=F5=B@0FVW F$ V, 7024O:8 V=0:B820FVW ;53:>3> ;0=FN6:0 :V=07878=C (MLCK), 4>
@>7A;01;5==O 3;04:>3> <'O70.
In vitro 4@>B025@@8= ?@83=VGCT 4VN D5@@<5=BC A?07<>;5@@8G=C $IV V =5 2?;820T =0 4VN V7>4V5AB5@02
D5@@<5=B8 III ($III) V D5@@<5=B8 V ($V). $IV <0T 25;8:V 4>@;8=V;:> 5
7=0G5==O 4;O 7=865==O A:>@>GC20;L=>W 0:B82=>ABV 3;04:8E <'O7V2, B>2V V=3V1VB>@8
FL;3> D5@@<5=B8 <>6CBL 1CB8 :>@8A=8<8 4;O ;V:C20==O E2>@>1, O:V AC?@>2>46CNBLAO
3V?5@@@CE;82VABN, 0 B0:>6 @V7=8E 70E2>@N20=L, ?V4 G0A O:8E 28=8:0NBL A?07@@8 H;C=:>2>-
:8H:>2>3> B@0:BC.
:;VB8=0E 3;04:8E <'O7V2 :0@@40 B0 AC48= F$ 3V4@>;V7CTBLAO 7451V;LH>3> V7>D5@@5=B>
$III, B>B025@@8= T 5D5:B82=8< A?07<>;5@@8G=8< 70A>1><, O:89 =5 <0T 7=0G=8E ?>1VG=8E
5D5:BV2 V7 1>:C A5@F52>-AC48==>W A8;@5<8 B5@@0?V8 C A5G>28284C @V7=8E FL;@@V, 4VW =0 FN
@>B025@@8= 5D5:B8289 ?@8 A?07<0E 3;04:8E <'O7V2, B>: V <'O7>2>3> ?>E>465==O. @>B025@@8=
4VT =0 3;04:C 2 <'O7V <VN@@C, 1V;V0@@V> <'O7V, A5G>AB0B52> <0 AC48==V <'O7V, =5570;56=> 2V4
B8?C WE V==5@20FVW 02B>=><=>N V==5@20FVT F==5@2CNG>N.
V= ?>A8;NT :;VB8==V @57C;LB0B8 C B0:V 3;04:V <'O7V A2>W 740B>@@V @>7H8@5==O 0G5:8=8.
$0@<0:>:V=5B8:0.
VO 4@>B025@@8=C T A8;L=>N 70 4VN ?0?025@8=C, 01A>@@@@@T 1V;L H5, I> =0 2V4
3> ?0@5=B5@0;L=>3> 22545==O =5 A?@8O0T@025<0TB0 B0;>>3> ?>1VG=V3>>3> 5D5:B8:. O: AB8
@@025@@8= H284:> B0 ?>2=V VABN 01A>@@@@>CTBLAO ?V4 G0A ?5@>@0;L=>3> 70AB>AC20==O. V=
28A>:>N N (95-98 %) 72O7CTBLAO 7 0;L1C<V% 22545=>W 4>78 =04E>48BL 4> :>=F5=B@0FVW 2 =57
5B01V>;V;V7CTBLAO 2 ?5GV=FV. 0?V2?5@V>4 1V2;@@3VGV=3VG=@>3> V03=3C20==O AB0=>28BL 8-10 3>4.
0 72 3>48=8 4@>B025@@8= ?@>0:B8289@=> ?>2=VABN 282@@48A@5BLAO 7 >@30=V7<C50 % 282@@48A@5CTBLAO V7
A5G5N B0 ?@81;87=> 30 % - 7 :0;><. >A=>2@025@@8= 282@@48AB5CTBLAO C D>@<@@

;V=VG=V E0@0:B5@8AB8:8
>:070==O
;V:C20;L=>N <5B>N ?@8:

- A?07<0E 3;04:>W 2O70=8E V7 70E2>@N20==O<8 1V;V0@=>3> B@0:BC: E>;5F8AB>;VBV07V, E>;0=3V>;VBV07V, E>;5F8AB8BV, ?5@8BE>;5F8AB8BV, E>;0=3VBV, ?0?V;VBV;
- A?07<0E 3;04:>W @N20==OE A5G>2>3> B@0:BC: =5D@@>;VBV07V, C@5B@@>;VBV07V, ?VT;VBV, F8AB8BV, B5=57<0E A5G>2>3>
/: 4>?>
- A?07<0E 3;04:>W 2>-:8H:>2>3> B@0:BC: 28@07:>2V9 E2>@>1V H;C=:C:0 B0 420=04FOB8?0;>W :8H:8, 30AB@@@8BV, :0@4V>- B0/01> ?V;>@@A?07<,VBV, A?0AB8G=>VBV V7 70?>@@>< V A8=4@@><>@07=5=>3> :8H5G=8:C, I> AC?@@>2>4>46CTBLAO <5B5>@87<><;
- 3>;>2=2=>;N =0?@@C65==O;
- 3V=5:>;>3VG=8E 70E2>@N20==OE (48A<5=>@5O).

@>B8?>:070==O.
V428I5=0 GCB;82VABL 4> 4@>B025@@8=C 01> 4> 1C4L-O:>W:>3> :@5=5=B0 ?@5?0@0BC. "O6:0 ?5GV4V=:>20, =8@@:>20 01> A5@F520 =54>AB0B=VABL(A8=4@@>< <0;>3> A5@F5230 28:84C).

A>1;82V 70E>48 157?5:8.
0AB>A>2C20B8 7 @>A>1;82>N >15@56=VABN ?@8 0@B5@V0;L=V9 3V?>B5=7VW.
>6=0 B01;5B:0 ?@5?0@@0BC @>B025@@8= 0 <3 @0:B8G=>. 5 70AB>A>2C20B8 4;O ;V:C20==O E2>@@8E, O:V AB@@0640NBL =0 @V4:VA=V A?04:>2V 70E2>@N20==O, B0:V O: =5?5@5>A8<VABL, 45DVF8B ;0:B078 01> A8=4@@>< <0;L01A>@1FVW 3;N:>78-30;0:B>78.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.
=3V1VB>@@8 D>AD>4V5AB5@078, B0:V O: ?0?025@@8=, 7=86CNBL 0@B5@V0;L=89 5D5:B ;52>4>?8. !;V4 7 @V4:VA=8<8 70AB>A>2C20B8 ?@5?0@0B @>B025@@8= >4=>G0A=> 7 ;52>4>?8=5NG=8<8, >A>1;82> 0 5@8>4 V=8FV0FVW B5@0?VW >A=>2==N@>=V5 5D5:B8 >48= 70E>48 ;V:020 7<5=HCNBL 0@B5@V0;L=89 B8A:.

A>1;82>3VABV @>B025@@8=.
0AB>A>2C20==O C ?5GVG>W B0 =8@@:>2>W =54>AB0B=>AB V.
>48 ?@>F5AV N@>DC=:FVW. /: ?5@@:0@?>8 @0?BC:LB0>08 @0:V0@A>A;8B0=8 :V;L::>AB> @V52465=L B0 4@@0;V52465=L =0 B@@0@0@8 @>1V:L, ?5@@@@0F5;;N@@@A?07, ?0@5=E8<0B>7=0 V5@0;V5>C<> 6>4@:3B5>@807 A?@0252V4:@8 =5 7@0B>AB8 1C4L-O:>W 0B>@@= ?@5?0@0BC @>B025@@8= ?@8 >:@5<0 ?>GVG>V4 B>:A8G=>@078 7 E2>@@V@>@8. '5@57 2V4ACB=VABL 40=8E @@>B025@@8= =5 70AB>A>2CNBL ?@8 ?>GVG>V9 B0 =8@@:>2V9 =54>AB0B=>AB =0 @V52V:LTCB5@87.

40B=VABV 2?;8205 =0 H240:LV5VABL @0B025@@8= B0 1C4L-O:V V=HV V?L5AV> ?@8 :5@@C20==V 02B>@@>1V;5< 7 V=8H8<8 5E0=V7<0<8.
/:I> C ?0FVT=B0 157 V=H8E 70E2>@N20==O ?@5?0@0B @>B025@@8= A?@8O205 70@C=8:@5=2>1FVW 70?<>@>G5==O, 2>=8 =5 B@@028@>28=C C:0@@=89 0 25@:>B2C 5257 5D5:B85@8G=>@= 70<>CB>, B@@>BV>6=>V< A?>;C@@8 02B>@@@@@875>66 V 28:@>A5>0G=> @>2@8;84, V?L?>B@@@= 2V5@ ?@8 @04V:0EL=8E A8B@@@@@@@@.

*!@>AV1 70AB>A>2C20==O B0 48. *
>@@=8:A;82 728G09=0 A5@4520 4>7> AB>A>2C25=5V4> 4:>B2V7<20C 70 2-3 ?@C689V8;
@07V 70AB>A>2C20==O 4@@@@025@@8=C 4VBO
4;O 4VB59 2V:@@ 6-12 @@@:V2 <0:A8<0;L=0 4>1>20 4>7> 70 AB>A>2C20B8 80 <3 (@@>7?>4V;57=0 =0 2 ?@C89@><;
4;O 4VB59 2V:@@ AB0@H5 12 @@@:V2 <0:A8<0;L=0 4>1>20 4>7> 70 AB>A>2C20B8 160 <3 (@>74V;57=0 =0 2-4 ?@C89@>?);

*VB8. *VBO< 2V:@< 4> 6 @@@:V2 70AB>A>2C20==O ?@5?0@0BC @>B8?>:070=>.*
0AB>A>2C20==O 4@@@025@@8=C 4VBO< =5 @5:><5=4C25BLAO C 72O7:C 7 2V4ACB=VABN 40=8E.

50<5>7C20==O.

!8<8: ?@8 7=0G=>7C20==V 4@>B025@8=C A?>AB5@V30;8AO ?>@CH5==O A5@F52>3> @8B 2V4=>ABV, 2 B>2=0 1;>:040 ?CG:0 VA0 B0 7C?8=:0 A5@FO, O:V<>6CBL 1CB8 ;5B0;L=8<8.
@8 ?5@54>7C20==V ?0FVT=B ?>28=5= 7=0E>48B8AO ?V4 @5B5;L=8< A?>AB5@565==O< ;V:0@O B0 >B@8

>1VG=V @50:FVW.
>1VG=0 4VO, I> <>6;82> 1C;0 A?@8G8=5=0 4@>B025@8=><, @>7??>4V;5=0 70 A8AB5<0<8 >@30=V2 B0 G0AB>B>N 28=8:=5==O: 4C65 ?>H8@5=V (> 1/10), ?>H8@5=V (> 1/100, < 1/10), =5?>H8@5=V (> 1/1000, < 1/100), ?>>48=>:V (> 1/10000, < 1/1000), 2:@09 ?>>48=>:V (< 1/10000).

1>:C VW A8AB5<<8: ?>>48=>:V: 0;5@3VG=V @50:FVW, 2:;NG0NG8 0=3V>=52@>B8G=89 =01@O:, :@>?82O=:C, 28A8?0==O, A25@1V6, 3V?5@5?0A8FN, >7==01, ?V428I5==O B5

1>:C A5@F52>-AC48==>W A8AB5<<8: ?>>48=>:V: ?@8A:>@5=5 A5@F518BBO, 0@B5@V0;L=0 3V?>B5=7VO.

1>:C =5@2>2>W A8AB5<<8: ?>>48=>:V: 3>;>2=89 1V;L, 70?0<>@>G5==O, 157A>==O.

1>:C H;C=:>2>-:8H:>2>3> B@0:BC: ?>>48=>:V: =C4>B0, 70?>@, 1;N20==O.

"5@ABV. 5 @>:V2.

#<>28 715@V30==O. 15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B5<?5@0BC@?=>=>=V

#?0:>2:0. > 10 B01;5B>:: C 1;VAB5@V,1 01> 3 1;VAB5@8 C ?0GFV.

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

8@>1=8:. " «8W2<54?@5?0@0B».

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A0 20465==O 4VO;L=>ABV.

#:@0W=0, 01032, 3>, 139.