

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

#"□ ""
(CUTIVATE')

!::04:

4VNG0 @5G>28=0: D;NB8:07>=C ?@>?V>=0B;
1 3 <07V =C ?@>?V>=0BC;
4>?>28=8: >;VO ?V;5=3;V:>;L, A>@1VB0=A5A:2V>;50B, 2VA::@8AB0;VG=89.

V:0@AL:0 D>@<0. 07L.

A=>2=V DV78:>-EVABV: >4=>@V4=0 =0?V2?@>7>@0 <07L 1V;>3> 01><0965 1V;>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0. >@B8:>AB5@>W48 4;O 70AB>AC20==O C 45@<0B>;>3VW. :B82=V
:>@B8:>AB5@>W48 (3@C?0). >4 "% D07A !17.

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

\$0@<0:>48=0

\$.NB8:07>=C ?@>?V>=0B T 3;N:>:>@B8:>W4=8< ?@5?0@0B<< 7 28A>:>N ?@>B870?0;L=>N
0:B82=VABN B0 4C65 =87L:8< @V2=5< ?@83=VG5==O 3V?>B0;0<<-.3V?>DV70@=>-
=04=8@:>2>70;>7=>W A8AB5<8 ?@8 AC20==V, B>3> B5@0?52B8G=89 V=45:A T >4=8< V7 =09H8@H8E
V7 CAVE =0O2=8E =0 40=89 G0A B>?VG=8E AB5@>W4V2.

\$.NB8:07>=C ?@>?V>=0B <0T 28A>:C A8AB5<=C 0:B82=VABL ?VA;O ?V4H:V@=>3> 70AB>AC20==O,
0;5 4C65 =87L:C 0:B82=VABL ?@8 ?5@>@0;L=>AC20==V, <>6;82> 7024O:8 <5B01>;VG=V9
V=0:B820FVW. >A;V465==O in vitro ?>:070;8 9>3> 28A>:C A?>@V4=5=VABL V7 3;N:>:>@B8:>W4=8<8
@5F5?B>@0<8 ;N48=8.

\$.NB8:07>=C ?@>?V>=0B =5 ?@>O2;OT =5?5@5410GC20=>3> 3>@<>=0;L=>3> 5D5:BC B0 ?>3> 2?;82C
=0 F5=B@0;L=C B0 ?5@8D5@8G=C =5@2>2V A8AB5<8, H;C=:>2>-.8H:>2C, A5@F52>-AC48==C 01>
48E0;L=C A8AB5<8.

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

IA>@1FVO.

@8 @0;L=>AC20==V 1V>4>ABC?=VABL 4C65 =87L:0 2 72O7:C 7 >1<565=>N 01A>@1FVTN
?@5?0@0BC G5@57 H:V@C 01> 7V H;C=:>2>-.8H:>2>3> B@0:BC B0 2 72O7:C 7 V=B5=A82=8<
<5B01>;V7<<< ?5@H>3> ?@>E>465==O. 5@>@0;L=0 1V>4>ABC?=VABL =01;860TBLAO 4> =C;O, B>
AC20==V <07V 1C45 =87L:8
>7?>4V;.

>A;V465==O ?@>45<=>AB@C20;8, I> A8AB5<=>W F8@:C;OFVW 4>AO30T 4C65 =57=0G=0 :V;L:VABL
?5@>@0;L=> 70AB>A>20=>3> D;NB8:07>=C ?@>?V>=0BC, O:0 H284:> 282>48BLAO 7 6>2GN B0
5:A:@5BCTBLAO 7 D5:0;VO<8. \$.NB8:07>=C ?@>?V>=0B =5 70B@8

5B01>;V7

0 40=8<8 D0@<0:>:V=5B8G=8E 4>A;V465=L =0 B20@8=0E, D;NB8:07>=C ?@>?V>=0B H284:>
282>48BLAO B0 ?V4;O30T 5:AB5=A82=>;V7 4> :0@1=>=>2>W :8A;>B8, O:0 <0T 4C65 =87L:C
3;N:>:>@B8:>W4=C B0 ?@>B870?0;L=C 0:B82=VABL.

82545==O.

0 40=8<8 4>A;V465=L =0 B20@8=0E, H;OE 282545==O =5 70;568BL 2V4 A?>A>1C 70AB>AC20==O
D;NB8:07>=C ?@>?V>=0BC. 82>48BLAO, 3>;>2=8< G8=><, V7 D5:0;VO<8, V F59 ?@>F5A ?>2=VABN
7025@HCTBLAO ?@>BO3<< 48 3>48=.

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

>:070==O.

>@>A;V.

5@<0B>78, GCB;82V 4> ;V:C20==O :>@B8:>AB5@>W40<8, B0:V O::

- 0B>?VG=V 45@<0B8B8;
- =C
- 2C7;C20B89 A25@1V6;
- ?A>@V07 (70 28=OB:>< ?>H8@5=>3> 1;OH:>2>3> ?A>@V07C);
- ?>@AB89 E@>=VG=89 ;8H09 (=59@>45@<0B8B), G5@2>=89 ?;5A:0B89 ;8H09;
- A51>@59=89 45@<0B8B;
- ?>4@07=N20;L=89 01> 0;5@3VG=89 :=B0:B=89 45@<0B8B;
- 48A:>W4=89 G5@2>=89 2>2G0;;
- 35=5@0;V7>20=0 5@8B@>45@40B:>289 70AV1);
- @50:FVO =0 C:CA8 :=<0E;
- G5@2>=0 ?VB=8FO.

VB8.

V:C20==O 0B>?VG=>3> 45@<0B8BC C 4VB59 2V:>< 2V4 3 2V4ACB=>ABV 5D5:BC 2V4 ;V:C20==O <5=H ?>BC6=8<8 :=@B8:>AB5@>W40<8.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> 4VNG>W @5G>28=8 01> 4> 1C4L-O:>3> :=5=B0 ?@5?0@0BC.

5;V:>20=V V=D5:FVW H:V@8.

>652V 2C3@8.

28G09=V 2C3@8.

5@V>@0;L=89 45@<0B8B.

5@V0=0;L=89 B0 35=VB0;L=89 A25@1V6.

!25@1V6 157 70?0;5==O.

5@<0B>78 C 4VB59 2V:>< 4> 3

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

C;> ?>:070=>, I> ACAC20==O 7 ?@5?0@0B0<8, I> <>6CBL V=3V1C20B8 CYP3A4 (=0?@8:;04,

@8B>=02V@, VB@0:>=07>); 30;LCYP3A4.

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

@5?0@0B 70AB>A>2C20B8 7 >15@56=VABN 4;O ;V:C20==O ?0FVT=BV2, 2 0=0<=57V O:8E 1C;8 ABV =0 :=@B8:>AB5@>W48 01> 1C4L-O:V 4>?>28=8. VAF52V @50:FVW 3V?5@GCB;82>ABV (482. @>74V; <<>1VG=V @50:FVW)) <>6CBL =0304C20B8 A8<8 70E2>@N20==O, O:5 ;V:CNBL.

0=VD5AB0FVO 3V?5@:>@B8F87< CH8=30) B0 72>@>B=>W AC?@5AVW 3V?>B0;0<>-3V?>DV70@=>- =04=8@:>2>70;>7=>W A8AB5<8 V7 ?@83=VG5==O< DC=:FVW =04=8@:>28E 70;>7 C 450:8E >AV1 <>65 1CB8 @57C;LB0B<< 71V;LH5=>W A8AB5<=>W 01A>@1FVW B>?VG=8E AB5@>W4V2. # @07V ?>O28 1C4L-O:8E V7 28I5=02545=8E A8AC20==O ?@5?0@0BC A;V4 ?>ABC?>2> ?@8?8=8B8 H;OE<< 7 <5=H5==O G0AB>B8 =0=5A5==O 01> 70

878:-D0:B>@0<8 28=8:=5==O A8AB5<=8E 5D5:BV2 T:

- ?>BC6=VABL B0 A:;04 B>?VG=>3> AB5@>W4C;
- B@820;VABL 70AB>AC20==O;
- =0=5A5==O =0 25;8:C ?;>IC H:V@8;
- 70AB>AC20==O =0 ?>25@E=OE H:V@8, I> AB8:0NBLAO, =0?@8:;04, C 7>=0E ?>?@V;>ABV 01> C :;N7V9=>W ?>2O7:8 (C =5<>2;OB ?5;NH:8 <>6CBL 2V4V3@020B8 @>;L >;N7V9=>W ?>2O7:8);
- ?V428I5=0 3V4@0B0FVO >@>3>2V;>3> H0@C;
- 70AB>AC20==O =0 4V;O=:0E 7 B>=:8< H:V@=8< ?>:@>2<<, =0?@8:;04 =0 >1;8GGV;
- 70AB>AC20==O =0 4V;O=:0E CH:>465=>W H:V@8 01> ?@8 V=H8E C<>20E, 45 A?>AB5@V30TBLAO ?>@CH5==O H:V@=>3> 10@ T@C.

>@V2=O=> 7 4>@>A;8<8 2 4VB59 B0 ?V4;VB:V2 <>65 01A>@1C20B8AO ?@>?>@FV9=> 1V;LH0 :V;L:VABL B>?VG=>3> :=@B8:>AB5@>W4C, V B>8 A?@89=OB;82VHV 4> A8AB5<=8E ?>1VG=8E 5D5:BV2. &5 ?>2O70=> 7 B8<, I> 4VB8 <0NBL =54>@>728=CB89 H:V@=89 10@T@ B0 1V;LHC ?>25@E=N H:V@8 2V4=>A=> <0A8 BV;0 ?>@V2=O=> 7 4>@>A;8<8.

VB8.

!;V4 C=8:0B8, 45 F5 <6;82>, 4>23>B@820;>3> I>45==>3> 70AB>AC20==O B>?VG=8E
:>@B8:>AB5@>W4V2 =5<2;OB0< B0 4VBO< 2V:> 4> 12 @>:V2, >A:V;L:8 C =8E 28I0 9<2V@=VABL
28=8:=5==O 04@5=0;>2>W AC?@5AVW.

V:C20==O ?A>@V07C.

0AB>A>2C20B8 B>?VG=V :>@B8:>AB5@>W48 4;O ;V:C20==O ?A>@V07C A;V4 7 >15@56=VABN,
>A:V;L:8 2 45O:8E 28?04:0E ?>2V4<>;O;>AL ?@> ?>O2C @5F8482V2, @>728B>: B>;5@0=B=>ABV,
@878: 35=5@0;V70FVW ?CABC;L>7=>3> ?A>@V07C B0 @>728B>: A8W 01> A8AB5<=>W
B>:A8G=>ABV, A?@8G8=5=8E ?>@CH5==O< 10@T@=>W DC=:FVW H:V@8. # @07V 70AB>AC20==O
4;O ;V:C20==O ?A>@V07C ?0FVT=B ?>28=5= 7=0E>48B8AO ?V4 @5B5;L=8< <548G=8< =03;O4>
0=5A5==O <07V =0 >1;8GGO.

"@820;5 =0=5A5==O <07V =0 H:V@C >1;8GGO T =51060=8<, >A:V;L:8 FO 4V;O=:0 T 2@07;82VH>N 4>
0B@>DVG=8E 7

0=5A5==O =0 ?>2V:8.

@8 =0=5A5==V <07V =0 ?>2V:8 A;V4 C=8:0B8 ?>B@0?;O==O ?@5?0@0BC 2 >GV, >A:V;L:8 F5 ?@8
?>2B>@=>AC20==V <65 A?@8G8=8B8 :0B0@0:BC V 3;0C:>
!C?CB=V V=D5:FVW.

)>@07C ?@8 ;V:C20==V 70?0;L=8E C@065=L, I> V=DV:>20=V, ?@87=0G0B8 2V4?>2V4=V
0=B810:B5@V0;L=V ?@5?0@0B8. # @07V ?>H8@5==O V=D5:FVW B>?VG=V :>@B8:>AB5@>W48
A;V4 2V42V4=C 0=B810:B5@V0;L=C B5@0?VN.

878: V=DV:C20==O ?@8 =0:;040==V >;N7V9=>W ?>2□07:8.

878: @>728B:C 10:B5@V0;L=8E V=D5:FV9 71V;LHCTBLAO 2 B5?;8E B0 2>;>38E C<20E, I> <6CBL
28=8:=CB8 ?V4 >;N7V9=8<8 ?>207:0<8, B>
%@>=VG=V 28@07:8 =V3.

=>4V B>?VG=V :>@B8:>AB5@>W48 70AB>A>2CNBL 4;O ;V:C20==O 45@<0B8BV2, I> 28=8:0NBL
=02:>;> E@>=VG=8E 28@07>: =V3. 4=0: B0:5 70AB>AC20==O 0A>FVNTBLAO 7V 71V;LH5==O<
G0AB>B8 28=8:=5==O @50:FV9 W 3V?5@GCB;82>ABV B0 71V;LH5==O< @878:C
/2=5 ?@83=VG5==O DC=:FVW :>@8 =04=8@:>28E 70;>7 (@0=:>289 @V25=L :>@B87>;C 2 ?;072V
<5=H5 70 5 20 3 ?@5?0@0BC =0 45=L.

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

03VB=VABL.

0=V I>4> 70AB>AC20==O D;NB8:07>=C ?@>?>=0BC 203VB=8< 6V=:0< >1<565=V.

VAF525 70AB>AC20==O :>@B8:>AB5@>W4V2 C 203VB=8E B20@8=<65 ?@872>48B8 4> 0=><0;V9
@>728B:C ?;>40, E>G0 2V4=>H5==O F8E 40=8E 4> 203VB=8E 6V=>: =5 2AB0=>2;5=>. 4=0:
?@87=0G0B8 D;NB8:07>=C ?@>?V=>0B 203VB=8< 6V=:0< A;V4 ;8H5 B>4V, :>;8 >GV:C20=0 :>@8ABL
2V4 70AB>AC20==O ?@5?0@0BC 4;O <0B5@V 1C45 1V;LH>N 70 <6;8289 @878: 4;O ?;>40 V 48B8=8.
0AB>A>2C20B8 =09<5=HC 5D5:B82=C 4>7C ?@5?0@0BC ?@>BO3< =09<5=H>3> <6;82>3> ?@>
>4C20==O 3@C44N.

57?5:0 70AB>AC20==O B>?VG=8E :>@B8:>AB5@>W4V2 C ?5@V>4 3>4C20==O 3@C44N =5
2AB0=>2;5=0. 52V4<>, G8 <65 70AB>AC20==O B>?VG=8E :>@B8:>AB5@>W4V2 ?@8725AB8 4>
B0:>W A8AB5<=>W 01A>@1FVW, 2 @57C;LB0BV O:>W C 3@C4=>4V 4>A;V465==O =0
;01>@0B>@=8E IC@0E ?@8 4>AO3=5==V 287=0G5=>3> @V2=O ?@5?0@0BC 2 ?;072V ?VA;O
?V4H:V@=>3> 22545==O 1C;8 28O2;5=V >7=0:8 =0O2=>ABV D;NB8:07>=C ?@>?V=>0BC 2 3@C4=>
@87=0G0B8 <07L D;NB8:07>=C ?@>?V=>0BC 2 ?5@V>4 3>4C20==O 3@C44N A;V4 ;8H5 B>4V, :>;8
>GV:C20=0 :>@8ABL 2V4 70AB>AC20==O ?@5?0@0BC 4;O <0B5@V 1C45 1V;LH>N 70 <6;8289 @878:
4;O 48B8=8. # @07V ?@87=0G5==O 2 ?5@V>4 3>4C20==O 3@C44N <07L =5 A;V4 =0=>A8B8 =0 3@C48
7 <5B>N C=8:=5==O 28?04:>2>3> ?>?040==O <07V G5@57 @>B 48B8=8.

\$5@B8;L=VABL.

0=8E 4;O >FV=:8 2?;82C B>?VG=8E :>@B8:>AB5@>W4V2 =0 D5@B8;L=VABL ;N48=8 =5<0T.

**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.**

>A;V465=L V7 282G5==O B0:>3> 2?;82C =5 ?@>2>48;>AL. >3;O4C =0 ?@>DV;L ?>1VG=8E @50:FV9
2?;82C =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 >GV:CTBLAO.

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

>@>A;VB0 4VB8 2V:>< 2V4 3

07L >A>1;82> A?@89=OB;820 4;O ;V:C20==O ACE8E ?>25@E>=L H:V@8, 0 B0:>6 H:V@8 7 ;8H09=8<8 01> ;CA>G:>28<8 C@065==O<8.

@5?0@0B =0=>A8B8 B>=:8< H0@>< =0 C@065=V 4V;O=:8 H:V@8 1 01> 2 @078 =0 4>1C. "@820;VABL ;V:C20==O ?@8 I>45==>AC20==V AB0=>28BL 4> 4 B86=V2 4> ?>:@0I5==O AB0=C, ?>BV< 7<5=H8B8 G0AB>BC =0=5A5==O <07V 01> 7

VA;O 4>AO3=5==O :>=B@>;N =04 E2>@>1>N G0AB>BC 70AB>AC20==O B>?VG=8E

:>@B8:>AB5@>W4V2 A;V4 ?>ABC?>2> 7<5=H8B8 4> ?>2=>W 2V4 V O: ?V4B@8A>2C20B8 5 <>;VT=B8.

>=>2;5==O A8W E2>@>18 <>6;825 ?@8 @0?B>2>AC20==O B>?VG=8E :>@B8:>AB5@>W4V2, >A>1;82> A8;L=>4VNG8E.

"@820;VABL ;V:C20==O 4>@>A;8E B0 ?0FVT=V2 ;VB=L>3> 2V:C.

@07V ?>3V@H5==O AB0=C 01> 2V4ACB=>ABV ?>:@0I0==O ?@>BO3< 2-4 B86=V2 4V03=>7 B0 ;V:C20==O A;V4 ?5@53;O=CB8.

VB8 2V:>< 2V4 3

4VB59 28I0 9<>2V@=VABL 28=8:=5==O A8AB5<=8E ?>1VG=8E @50:FV9 ?@8 70AB>AC20==V B>?VG=8E :>@B8:>AB5@>W4V2, B<< W< ?@87=0G0NBL :>@>BHV :C@A8 ;V:C20==O B0<5=H ?>BC6=V ?@5?0@0B8, =V6 4;O 4>@>A;8E.

07L CBV259B 70AB>A>2C20B8 7 >15@56=VABN 4;O 70157?5G5==O =0=5A5==O

"@820;VABL ;V:C20==O 4VB59.

/:I> ?@8 70AB>AC20==V <07V 4VBO< ?@>BO3<< 7-14 4=V2 =5 =0ABC?0T ?>:@0I0==O, ;V:C20==O A;V4 ?@8?8=8B8 B0 48B8=C 4>>1AB568B8. /:I> ?@>BO3<< 7-14 4=V2 ;V:C20==O 4>AO30TBLAO :>=B@>;L 70 70E2>@N20==O<, 40;V A;V4 70AB>A>2C20B8 AC20==V =5 ?>28==0 ?5@528IC20B8 4 B86=V.

0FVT=B8 ;VB=L>3> 2V:C.

0 40=8<8 ;;V=VG=8E 4>A;V465=L =5 1C;> 28O2;5=> @V7=8FV C 2V4?>2V4V =0 ;V:C20==O AO3=5==O 1060=>3> @57C;LB0BC.

5GV=:>20/=8@:>20 =54>AB0B=VABL.

@07V A8AB5<=>W 01A>@1FVW (?@8 70AB>AC20==V =0 25;8:V9 ?>25@E=V B0 ?@>BO3<< B@820;>3> G0AC) <5B01>;V7< B0 5;VAO3=5==O 1060=>3> @57C;LB0BC A;V4 70AB>A>2C20B8

VB8. 0AB>A>2C20B8 4;O ;V:C20==O 4VB59 2V:>< 2V4 3

5@54>7C20==O.

!8<8.

\$.NB8:07>=C ?@>?V>=0B ?@8 AC20==V <>65 01A>@1C20B8AL C :V;L:>ABV, 4>AB0B=V9 4;O 28=8:=5==O A8AB5<=>3> 5D5:BC. >AB@5 ?5@54>7C20==O T <0;>V<>2V@=8=VG=>3> ?5@54>7C20==O 01> 7;>26820==O <>6CBL 28=8:=CB8 >7=0:8 3V?5@:>@B8F8774V; <<>1VG=V @50:FVW»).

V:C20==O.

@07V ?5@54>7C20==O 70AB>AC20==O <07V A;V4 ?>ABC?>2> ?@8?8=8B8 H;OE<< 7<5=H5==O G0AB>B8 =0=5A5==O 01> 70N =0 <5=H ?>BC6=89 B>?VG=89 :>@B8:>AB5@>W4, 72060NG8 =0 @878: @>728B:C 3;N:>:>@B8:>AB5@>W4=>W =54>AB0B=>ABV. >40;LH5 ;V:C20==O ?@>2>48BLAO 2V4?>2V4=> 4> ;;V=VG=>3> AB0=C ?0FVT=B0.

>1VG=V @50:FVW.

>1VG=0 4VO ;;0A8DV:>20=0 70 >@30=0<8 V A8AB5<0<8 B0 G0AB>B>N 28=8:=5==O. '0AB>B0 28=8:=5==O ?>1VG=8E 5D5:BV2 287=0G0TBLAO 70 B0:8<8 :@8B5@VO<8: 4C65 G0AB> (□1/10), G0AB> (□1/100, □1/10), =5G0AB> (□1/1000, □1/100), @V4:> (□1/10000, □1/1000), 4C65 @V4:> (□1/10000), 2;;NG0NG8 ?>>48=>:V 28?04:8.

=D5:FVW B0 V=207VW.

C65 @V4:>: >?>@BC=VAB8G=V V=D5:FVW.

I>:C VW A8AB5<8.

C65 @V4>: 3V?5@GCB;82VABL.

I>:C 5=4>:@8==>W A8AB5<8.

C65 @V4>: ?@83=VG5==O 3V?>B0;0<>-3V?>DV70@=>=-04=8@:>2>70;>7=>W A8AB5<8:

- 71V;LH5==O <0A8 BV;0/>68@V==O;
- 70B@8ABC <0A8 BV;0/70B@8ABC C 4VB59;
- CH8=3>W4=V >7=0:8 (4V1=5 >1;8GGO, F5=B@0;L=5 >68@V==O);
- 7<5=H5==O @V2=O 5=4>35==>3> :>@B87>;C;
- 3V?5@3;V:57C@VO;
- 0@B5@V0;L=0 3V?5@B5=7VO;
- >AB5>?>@>7;
- :0B0@0:B0;
- 3;0C:><0.

I>:C H:V@8 B0 ?V4H:V@=>W B:0=8=8.

'0AB>: A25@1V6.

5G0AB>:

C65 @V4>: ?>B>=H5==O H:V@8, 0B@>DVG=V A7, 3V?>?V3<5=B0FVO, 0;5@3VG=89 :>=B0:B=89 45@<0B8B, 703>AB@5==O 45@<0B>7V2, 3=V9=8:>289 ?A>@V07, 5@8B5<0, 28A8?0==O, :@>?82O=:0.

"5@ABV.2 @>:8.

#<>28 715@V30==O. 15@V30B8 ?@8 B5ABC?=>

#?0:>2:0. > 15 3 <07V 2 0;NN <5<1@0=>N B0 ?>;V?@>?V;5=>2>N :@8H5G:>N C :0@B>==V9 C?0:>2FV.

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

8@>1=8:. □;0:A>!

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VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.

□;0:A>!

189, 2C;. @N=20;L4AL:0, 60-322 >7=0=L, >;LI0/

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