



Fig. 1., I G.8JG:D; J 8JB>C

AO=>B: 6H9H6H:)6G@CHD9H6H: 6C9 IJ C>GIDC9H6H: J G=>GBDG: 8J8JB>C=6H7: :C H>DLCIDAB>I 8ND@G: GA6H 6C9 >H D; ED: C>A7: C: >I >C I=: IG6IB: C I B>8D7>6A>C: 8I>DCHB: 9>6I:9 7N 768I: G6 6C9 K>GJH

: HE I :K>: C8 ;DB in vitro 8:AA8JAJG: 6C9 EG8A>G86AHU9>:H >C6C>B6 AH8A>G86AHU9>:H=6K: CD ECK9: 9 HGID< :K>: C8 ;DG6 I=:G6E:J I>8: ;: 8I D;8J8JB>C 4 5 =>H>H@ANJ: ID>HEDDGE=6C6 8D@G:I>8 EDEG>H AS@ IDJC6IIG8K: E=NH>B6A8=>B >86AEDEG>H H,B=6HEDDGFJ: DJHHI>N 6I E=NH>DAB>86AE! 8=>B >86A>G6I>6A >N B: I67DA>H67>N EDDG6A7HEDC6C9 G6E: :A>B>C6>D>C6A D; L=>8> 8D@G>7I: ID AD HMI: B>8 8D@: CIGI>DCH 6C9 AB>I9 7AD9E7G>C 76G>G E: G: 67>AN4 6C9 G:;GC8: H8>: 9 I=:G>C5 H 6 8DCH>FJ:C8: H>K>G6AII: BEIH=6K: 7: :C B69: ID>BEOK HMI: B>8 AK>AHD; 8J8JB>C;DAAD>G 9DH>G JH>G ;DGBJ A6>DC6EEDEB=:H I=6I G6< :DB 8DB EAM6I>DCL>I= 69?K6CIH6C9 >GAIHDB>CC6CDE6> 8AH AEDHIB: H 6C9 E=DHE=DAE>9 B>8:AAH ID I=: 9: H>C D; CDK:A 6C6A>4H>I= 7: II: GD6A67HEDC4 5 &DG: G8: CIAN6 CJB 7: GD; >OK: H>6IDGH>6K: 8A>B: 9 I=6I I=: A6@D: ;: >868N7N8J8JB>C>H: C>C CJB: DJH8A>G86AIG6A>H9J: ID I=: ;68I I=6I >I>H6)6 C HH@N"CI: G: G :C8:) " ' , 8DB EDIC9 L=>8> ;G FJ:CIAN<K: H;6AHEDH>K: GHJAH 9JG>G I: H>G 4 5 8-6G8I: G>H8 D; I=>HNE: D; 8DB EDIC9 >H=6I >I >HCD 9>G8I:9 IDL6 G96 HG<A BDA8JA6I6G: I 7J1 6<6>C>H B6 CN 9>H E6G6 I6G: IHD9>H6 H H O: =6K: CD: 9 I=6I ' ü ' J8A6 G;68IDG @EEB >HJEEGH:9 7N8J8JB>C>C>C6B B6I>D8 86C8: G6C9 B6 CN DI=: G9>H6 H4 D5 (I I=:GH=6K: B69: HB >A66G>B: CIH CD>G 8JG 8JB>C 86C6; ;: 8I B6 CN9>; GCI <: C: H4 5 + : 8: CI 8A>G86AHU9>:H =6K: H>DLC I=6I I=: ;>AG D; ;6>G 8A>G86AIG6A>H9J: 8J8JB>C 8DB EDIC9HL6 H9J: ID I=: >G7>AN>Q=:H: HU9>HID68=>K: 69: FJ6I: 7AD9 AK>AHD; 8J8JB>C "C9: :9 8J8JB>C>HEEDGHMI: B>8 :MEDHJG: ;DAAD>G DG6A69B>C>H6I>DCH>K: HHI=6I I=:G >H6 C: :9 ;DG=>=:G 6C9 BDG: HJH6>C9 ESH6 AK>AHD; 8J8JB>C ID DB>B>O: >HIG6IB: CI :; ;: 8I H=>JH >I=6H7: :C H>K: HI9 I=6I =>=:MEDHJG: D; I=: <6HCD> I: HICAI68I ID 8J8JB>C; DAAD>G DG6A69B>C>H6I>DCB N ECK9: I=:G6ENL>I= GHEB I ID <6HCD>: HIC>A68C8: G8C9 >OK: CDIJH69B>C >H6I>DCCD; ;DGBJ A6: 9 8J8JB>C B6 NECK9: =>=:CDJ<= ESH6 AK :AHD; 8J8JB>C;DGHMI: B>8 IG6IB: CI 4 5 G:>A I 6A>O6 86C8: GHU9N JH>G :H86A>G 9DH>H D; 6C >OK: CDIHAN69B>C>H G9 AEDH6A EGE6G6>DCCD; 8J8JB>C L: G: 67A: ID 68=>K: 7AD9 AK>AH I>B: H I=6I D; H6C9G9D6A8J8JB>C 4 5 8A6 G9DH>EGHEDH: L6 HH>C L>I= G9J8I>DGH>C6C8: G6G @H 86G>CDB 7D>G>86Q<: C E@H6I: HE8>>86Q<: C H>C D@AN6I I=: =>=:HI 9DH>H D; AEDH6A 8J8JB>C 69B>C>H G9 J G=:GBDG: 6H6 8DCH>FJ:C8: D; >HEDDGE=6C6 8D@> C: I>8I I=:G =6H7: :C 8DCH>G67A: HE8 JA6>DC6HID L=: I=: G8J8JB>C DG>HB: I67DA>H6G GHEDH>A ;DGI=: in vivo 68>K>ND; 8J8JB>C 4 5 "I I>H=:G ;DG:>BED6CI ID <6C6 7: II: GJC9: G6C9>G D; I=: GA6 I>DCH>E7: IL :; C16G: IH>9CI>9 ;DG8J8JB>C in vitro 8:AA8JAJG: 6H H@NH 8J8JB>C>HE=6C6 8D@G: I>8I6C9 I=: 68>K>ND; 8J8JB>C 6I >H I6G: IH in vivo

"CI I=>HGK>L L: =6K: >OK: H>6I: 9 I=: C6JG: D; I=: GA6>DCH>E 7: IL :; C I=: in vitro 8:AA8JAJG: ;: ;868N E=6C6 8D@G: I>8I6C9 in vivo ;: ;868ND; 8J8JB>C>CEG8A>G86ABD9>AHD; 86C8: G6C9 >C6B B6 IDGN 9>H6H: H E6GID; I=>H>OK: H>6I>DCC6C9 ;DGH EA>8 N L: =6K: B69: I=: 6HH>BEI>DCI=6I 8J8JB>C>HEBDHIED: CI IG6IB: CI ;: ;: 8IH6G 6HID 8>6I:9 L>I= I=: E6GCI BDA8JA: 6C9 6G A>H>A@AN6HHI>6I:9 L>I= >H B: I67DA>H 6A>DJ<= 8A6 GM H>K>G6AD; 8J8JB>C>HE: I67DA>H >: I: IG=>N9D8J8JB>C - ! 9DEDH>HHI>B: 7>D6I>K>N 4 5 ' ü L6H

8=>H>C 6HI=: I6G: I 7DI=> >C8: A>8JAJG: 6C9 in vivo <K: CI=: ;68I I=6I 8J8JB>C=6H7: :C L: A>G>H>6G=>9 6H6C >G>7>DGD; ' ü 4 D 6C9 G: ;GC8: H8>: 9 I=:G>C56C9 I=:G :M>H6 HJ7H6C>6A6B DJCI D; >CDB6I>DC>CI=: A>G6IJG: E: G6>G>G ID 8J8JB>C>HE>G>7>DC' ü B: 9>6I:9 GHED>H>C 8: AA8JAJG: 6C9 >H 6C>86C8G 6C9 6C> >C6B B6 IDGN; ;: 8IH in vivo)A6H7A :ME6C6>DCH6C9 G6>DC6A: 6G ECK9: 9 ID AS @=: 8: A>8JAJG: 68I>K>ND; 8J8JB>C 6I ' ü L>I= >H E=6C6 8D@G: I>8I6C9 in vivo IG6IB: CI :; ;868N>CEG8A>G86ABD9>AHD; 86C8: G6C9 >C6B B6 I>DC

2. Evidence for an interaction of curcumin with NF-κB: Studies in cell culture

=: C>8A6 G I6CH8E I>DC ;68IDG' ü >H6 I6CH8E I>DC ;68IDG ;DJC9 >CI=: 8: A>8NDH>D; 6 L>9: K6G>ND; 8: A>6C9 G<JA6 HI=: :M EGH>H>CD; 9>H>C8 H>HD; <: C: HI=6I :C8D9: ECI: >G>OKA9 >CB: 9> 6I>G>6 CJB 7: GD; 8: A>A6>J C8>D>G>G>A9>G 8: A>A6E6A>G6I>DC >C ;6B B6 IDGN>HEDH>H 6C9 8: A>A69=: H>C4 5 "I >H=:G ;DG: 6 I6G: I D; >OK: GHI ;DG I=: 9: K: ADB: CI D; 6C>86C8G 6C9 6C>>C6B B6 IDGN 9G<H =>; ;C8>D>G>AN68>K: ' ü :M>H6>C>AN6H6 =>: I:GD9>B: G 8DCH>H>G D; E 6C9 I=: E@ID D@D: C: G %6HHI>6I:9 ECI: >G L=>8> 6G CDB6 AM H>FJ: HI: G9 >CI=: 8NDH>A6H6C>G8>K: 8DB EAM 7N7>C9>G ID I=: >G>7>DGNECI: >C' ü 'y =DHE=DGM6>DC6C9 HJ7H: FJ: CI J7>F>C8>DCCD; "ü 'y JEDC: MEDHJG: D; 8: A>AID K6G>DJH: MI68: A A>A6H>B>A>A69HID 6 G6E 9: <G96I>DCCD; I=>H>G>7>DGNH>JJC>I7N ECI: DHIB: H =>: GHJ>A>G ;G: ' ü IGCH8E6I: H ID I=: C>8AJ H L=: G: >I7>C9H ID I=: HE8>>8 I> 7>C9>G H> HI=6I 6G AB6I: 9>Q=: E@ BDI: GG<>DCCD; I=: I6G: I <: C: H I=: G7 N 8D@G AS<I=:>G: ME>GH>C 4 D 5

CJB 7: GD; HU9>:H>C8JAJG 9 8: A>A=6K: >I=:GECK9: 9: K>9: C8 :>I=:G ;DG8J8JB>C>HE>G8I >G>7>DCCD; ' ü DGBJ8JB>C>HE>G>7> I>DCCD; I=: :ME>GH>CD; <: C: E@9J8IH G<JA6 9 7N' ü >: 8N ID@G: H 8=>B D@CH : C: G6AN I=: ED: C8N D; 8J8JB>C ID >G>7> I=:H E@8HH>HG<H; ;DB I=: AD ID=>=:B>8DGD68D8: CIGI>DCH I=6I 6G CD 6HHI>6I:9 L>I= 6 8NDIDM8 :; ;: 8I D; 8J8JB>C 6 I6 8D@: 8: G6G 8J8JB>C>HE>G8I >G>7>DCCD; ' ü 6C9 >G>7>DCCD; 8N ID@G: 8=>B D@C GA6H >HEGH: CI 9 >C67A (I I=: GHU9>:HCD >C 8A9:9 >C-67A =6K: 6A>H8=6G8: G>@ I=: >G>7>DCCD; ' ü 7N 8J8JB>C J 8JB>C 6I 8D@: CIGI>DCH G6<G>G ;DB ID Z& L6H ;DJC9 ID >G>7> (I I: G6: 86C>D>E=D>GDA 68I 6I: >GJ8: 9 68>K6 I>DCCD; ' ü 7N EGK: C>G I=: 9: <G96I>DCCD; I=: >G>7>DGNECI: >C "ü 'y 6C9 I=: HJ7H>FJ: CI IGCH8E6I>DCCD; I=: G %6HHI>6I:9 HJ7J>IID I=: C>8AJ H>C8JAJG 9 =JB6 C E@BN: A>BN>8 AJ@B >68: A>A6C9 7N 6 9>G8I >OK: GEI>DCCD; I=: 7>C9>G D; ' ü ID >H8DCH>CH>H' H: FJ: C8: H4 5 .H>G 6C>OK>D BD9: AD; =JB6 CI: CDBN: H 8J8JB>C 6I 8D@: CIGI>DCH; D Z& >G>7>I9 "% p>GJ8: 9 >C6B B6 I>DCC6C9 6EDBDH>C8JAJG HD; =JB6 CI: CDBN: H7N 7AD>G>G' ü B: 9>6I:9 9DLC G<JA6>DCD; <: C: E@9J8IH I=6I B: 9>6I: B6I>GM9: <G96I>DC B 6I>GM: I6A>E@I: >G H 6C9 E@H6C>9 E@9J8I>DC 8N 8ADMN: C6H: 6C9 6EDBDH : A>A6 E=6B6 6HHI>6I:9 1)GD I: >C6C9 68>K6: 9 86>E6H: 4 5 "CI=: H6: HU9N 8J8JB>C 6I 6 8D@: CIGI>DCCD; Z& HJEEGH:9 "% p>GJ8: 9' ü 68>K6>DCK6 >G>7>DCCD; E=DHE=DGM6>DC6C9 9: <G96I>DCCD; >G>7>DCCD; "ü 'y >G>7> I>DCCD; "ü @G>H: 68>K>N 6C9 >G>7>DCCD; I=: C>8A6 G I6CH8E6I>DCCD; ' ü .H>G FJ6C>6I>K:) + 6C9 ;ADL 8NDB: IGN 8J8JB>C Z& L6 H H>DLC I>G6H: I=: 8=>B DI=: GE: JI>8 :; ;: 8IH D; E@C H>ID: IB: G6EIDEJG C 9: M6B I=:6HID: 8N>A>E=DHE=6B>9 A6HEG6>C6H: K>C8G>HC: 96JCDG7>8>C 9DMDG7>8>C B: I=DIGMI: 6C9 8N6G67>C: >C 6C68J: A>B E=D7A>H>8 AJ@B >68: A>A6: K6: C=6C8 B: CID; 86>E6H: ü 6C9 9DLC G<JA6>DCD; C>8A6 G' ü 68>K6>DC

-6 @CID: I=:G HU9>:H>C8JAJG 9 8: A>A>G>86I: I=6I 8J8JB>C E@ 9J8: H9>G8I >G>7>DCCD; ' ü GHJ>A>G >C6C >G>7>DCCD; ' ü 9: E: C9CI 8ND@G: 8=>B D@C <: C: :ME>GH>CD (; E6G>8JA6>BED6C8 L>I= GHEB I ID I=: >G>7>DCCD; ' ü 7N 8J8JB>C>H=: 9DH: 9: E: C9C8: D; >H>G>7>DCCD . C ;DJC6: ANB6 CN

Table 1

: 8G6H9' ü 8I&K6>DC6C9 NID@S: 6C9 =:B D@C +: A6H &: 9>6I:9
7N J @JB>C>C: AAJ AJG:

J AJG9 : A#6C9 -G:6IB :CI	C9ED&I	DC8CIGI>D&D; J G8B >C6C9 "C=>7>D&D;" ü	+:: G:C8
' ü G:6HI86G8@B6	8 I&K6>D&D;" ü	Z& 6C9 ü 4 5 ' ü 68I&K6>DC>C IL D7G6HI86C8G8:AA A6:H	
&DJH B68@E=6<:H		6C9 Z& 6C9 ü' ü 68I&K6>DC GHEB1K:AN	4 5
IJ B6CBDC@N: H		6C9 Z& EG :MEDHJG: 6C9 ü ' ü 68I&K6>DC JEDC:MEDHJG:ID H&BJAH GHEB1K:AN	4 5
"CI: H&@A:E>E: A6A 8: A#		Z& ü' ü 4 5 68I&K6>DC Z& ü' ü 4 5 68I&K6>DC Z& ü' ü 4 5	
)GDH6I: 86C8G8: A#		68I&K6>DC7N :>=:G 8NDH&: 6@7>D&H9 D&:- 1	
"CI: H&@A:E>E: A6A 8: A#		Z& ü' ü 4 5 68I&K6>DC	
IJ B6C': JIG@=>#		Z& ü' ü 4 5 68I&K6>DC	
NID@S: 6C9 =:B D@C +: A6H &DJH B68@E=6<:H	' ü " % p 6C9 % GA6H >CGH@D&:ID A&E&D&N@8=6G9: 8=6A&C<	6C9 Z& 6C9 ü' ü 6C9 ü' ü GHEB1K:AN	4 5
&DJH B68@E=6<:H	"% 6C9 -' ü GA6H >CGH@D&:ID 8DC@8K&S 6C9 A&E&D&N@8=6G9: .E G<JA&D&D; 8=B D@C A#6C9 1 % ;D&BL>G >C: 8I>D&L>I= C&D >CAJ: C@:	Z& ü' ü ü' ü 6C9 Z& 6C9 ü' ü 6C9 ü' ü 6C9 Z& 6C9 ü	4 5
&>99A: :6G:E>E: A6A 8: A#>C: 8I:9 L>I= C&D INE: 67A: =6: B DE=>AJH >CAJ: C@:		6C9 Z& 6C9 ü 1 % GHEB1K:AN	4 5
&DJH H&A:C8 B68@E=6<: HIG6I: 9 L>I= %E&D&N@8=6G9:	"% E@9J8I>DC	6C9 Z& 6C9 ü' ü GHEB1K:AN	4 5
IJ B6CBDC@N: H	"% " % -' ü E@9J8I>DC	6C9 Z& 6C9 ü' ü 6C9 ü' ü 6C9 Z& 6C9 ü	
"CI: H&@A:E>E: A6A 8: A#	"% B: 9>6I:9 % H:8G >D&	' ü 6C9 Z& 6C9 ü' ü GHEB1K:AN	4 5
)GDH6I: 86C8G8: A#	=:B D@C G8:EIDG 1 + :A&K6I>D&	Z& ü 1 + Z& ü &) 6C9 ü' ü 6C9 ü' ü	4 5
"CI: H&@A:E>E: A6A 8: A#	&) -' ü E@9J8I>DC	Z& ü &) 6C9 ü' ü 6C9 ü' ü	
IJ B6C': JIG@=>#	"% E@9J8I>DC	Z& ü' ü 4 5	

D; I=: HU9>:HB: C>D&C9 67DK JH9 :>I=:G 6 H&<A DGL D 8DC8: CIG
I>D&D; 8J@JB>C !D L :K:G ;DGI=: HU9>:H8DC9J8I:9 7N>@:H<6IDGH
:B E&N&G BDJH B68@E=6<:H4 5 T A#E=D&N: H6C9 B68@E=6<:H
4 5 H&A:C8 B68@E=6<:H4 5 B>99A :6G:E>E: A6A8: A# 4 5 6C9 =J
B6CBDC@N: H4 5 8J@JB>C 9: 8G6H9' ü 68I&K6>N>C6 8DC8: C
IGI>D&D; 9: E: C9C1 B6CC: G -D ;JG=: G :ME&D G I=: 8DC8: CIGI>D&D
9: E: C9C8: D; I=: ;: 8IHD; 8J@JB>C >C8: A&AJAJG: I=: >C&D&6I>D&C
EGH:C:9 >C-67A L6H>AJH&I:9 7N8D&H&G:8I>G: H&B1: @E&D&H&D; I=:

-67A continued

J AJG9 : A#6C9 -G:6IB :CI	C9ED&I	DC8CIGI>D&D; J G8B >C6C9 "C=>7>D&D;" ü	+:: G:C8
)6 C8G6I>886G8@B6 8: A#A&:H	"% GA6H	I " 8DC8CIGI>D&D; 8JG8B >C:DG >G=>7>D&D; 8: AA <@LI= >C;K: 8: AA A6:HD; 6C9 Z& 6C9 ü' ü GHEB1K:AN	4 5

ü "C=>7>D&D;

8DC8: CIGI>D&D; 8J@JB>C>C8: A&AJAJG: K: GH: I=: 8J@JB>C: B: 9>6I:9
E: @: C19: 8G6H: D; :>I=: G9>G8I 68I&K6>D&D;" ü DG ü 8ND@S:
8=B D@C GA6H >< DI=: ;DG9>G8I >G=>7>D&D;" ü 6C9 >G=>
7>D&D; 8ND@S: 8=B D@C GA6H AD: G8DC8: CIGI>D&D; 8JG
8JB>C E@9J8: 9 6 L>9: G@< D; >G=>7>D&D; ADL: G ID =<=<:G L= >8
I: C9:9 8A6 G&IDL6 G9H6 =<=<:G>G=>7>D&D;HI=: 8: A&AJAJG: 8DC8: CIG
I>D&D; 8J@JB>C >G6H:9 -=>HHJ<: HH I=6I 6 8DC8: CIGI>D&D
9: E: C9C8: ;DGI=: 9>G8I >G=>7>D&D; >G=>7>D&D; 6C9 D; 8ND@S:
8=B D@C GA6H 7N8J@JB>C9D&H: M>HH I=: A6I: GEDH7&ANG68=>G
6C6EE6GC1 B6MBJ B L>I= >G6H:G 8DC8: CIGI>D&D; 8J@JB>C -=:
HB >A&8DC8: CIGI>D&D; < D; 8J@JB>C ;DG9>G8I >G=>7>D&D;" ü

Fig. 2. +: A&DGH=>E: IL:: C I=: D C8: CIGI>D&D; J @JB>C>C: AAJ AJG:
6C9 >I=: G I=: ;: 8I D; J @JB>C D&D;" ü DGNID@S: +: A6H -=: 8DC8: C
IGI>D&D; 8J@JB>C>C8: A&AJAJG: H&@L C>C-67A L: G: E&D: I: 9 6<6<C&H I=:
8J@JB>C: B: 9>6I:9 9: 8G6H&D; 68I&K6>D&D;" ü E6CA D&N@S: G:
A6H E6CA

609 8ND@G: 8=B D@C GA6H >HDDCH: CIL>I=I=: G@A: D; ' ü >C 8DCI@AG<I=: :MEGH@CD; 8ND@G: <: C:H>CI=: 8: AA=-: 606AHH EGH:CI:9 =: G:>H6AHDH.EEDG19 7NH:K:G6AHU9>:H>@86I>G 6 8DD8: C I@>DC9: E:C9:CI :; : 8I ;DG8J@JB>C6I ' ü

"C 699>DCID 9: BDCHG@>G I=6I 8J@JB>C 8DJA@ >G>7' ü >C 8: A@JAJ G:>C6 8DD8: C I@>DC9: E:C9:CI B6CC: G GHJAH; @B H:K:G6A HU9>:HH:K<: HII=6I I=: >G>7>DCCD; ' ü 7N8J@JB>C B6N7: AID< AK:9 6C9 EDH7AN>GK: GHTA: =->HE@EGIN D; 8J@JB>C L6 H8A6 GM 9: BDCHG@ 9 7NI=: LDG@; \$C<:I 6A 4 5 JH>G T AIB E=D8N: H6C9 B68DE6<: H "C 699>DC 6C 6EE63CI AID<AK:9 >GK: GHTA: 68I>N L6 H6AHD: 9; DG8J@JB>C L>I= GHE8I ID I=: <DLI= 6G@HID; 8-GID:8 BN:AD< CDJHAJ@B >6AIB E=D7A@H>8 \$ 8: A@H6H 8DCH: FJ: C8: D; 8J@JB>C @H68I>N DCI=: +(, G 68I>K: DMK: C HEB>: H B: I67DA8 E@=L6 N "CI=>HHU9N 8J@JB>C 6C9 >B6I>C7 7DI=: L: G: H>DL CIDHJE EGH I=: E@A>G6I>DCCD; \$ 8: A@H ID L: K: G 6I: GG BDK6AD; 8DB EDJC9 8: A@H6I: 9 L>I= >B6I>C7 H6G: 9 IDE@A>G6I: 6<6<C L=: G6H 8J@JB>C IG6I: 9 8: A@H B6>C9 <DLI= >G>7>: 9 6C9 <G9J6A@NADH I=: >GK: 67>A N 4 5 =: ED: CI>6A; DG6 AID<AK:9 >GK: GHTA: >C: G@8 I>DCCD; 8J@JB>C 6I I=: 8: A@K: AB6N; >JG 8G I@8A@>C=: G A@>DCH>E 7: IL : C I=: E=6@68D@G: I>@HD; 8J@JB>C 6C9 >H: ; >868N6I ' ü in vivo 'D 8A6 GB: 8=6C>HB; DG I=: E@9J8I>DCCD; 6 AID<A@H>G>G>7>DC D; ' ü L6 HEGH: CI: 9 =DL :K: G >I=6H7: :C HEBJAH: 9 I=6I 8J@JB>C B6N8=: B >8A@H G68 6C9 >GK: GHTA@ND9>N I=: E@I: >@I>I6H@B: 6I: H L>I= >: K6 6A@N@>DCCD; 8G I@8A6B>D 68>9GH9J: H 4 5 J G 8JB>C @HED: CI>6AIDE@J8: 9 6AID<AK:9 >GK: GHTA: >C: G@8I>DC6I >H I6G: I B6N 8D@G: 7I: I=: 6EE63CI ED: CI :; : 8I D; 8J@JB>C D7 H: G@9 >CHIB: 8: A@JAJ G: HU9>: H "C HJB B6GN>C8: A@JAJ G: 8JG 8JB>C 9>G8IAN>G>7>H' ü 6C9 ' ü B: 9>6I: 9 :MEGH@CD; 8N ID@G: H6C9 8=B D@CH 8DD8: C I@>DC9: E:C9:CI B6CC: G6C9 6I 8DD 8: C I@>DCHG@>G; @B ID Z& J @JB>C 6AHD=6HI=: ED: CI>6A ID E@9J8: 6 AID<A@H>G>G>7>DCCD; ' ü

3. Cellular uptake of Curcumin: Impact on the inhibition of NF-κB

(; GAK6C8 ID69>8JH@CD; I=: GA@>DCH>E7: IL : C I=: 8: A@JAJ IJG: 8DD8: C I@>DC9: E:C9:CI 68I>K>ND; 8J@JB>C 6H6' ü >G>7>DG 6C9 8J@JB>C H68I>K>N in vivo >H6 9>8JH@CD; L=6I >H8J@CIAN @DLC 67DJ I=: 8: A@H6 JEI6@: D; 8J@JB>C GDB I=: EG8: 9>G 606AHH>I L6 HD7H: G@9 I=6I 8J@JB>C >G>7>I9 ' ü 6C9 ' ü 9: E:C9: CI 8ND@G: GA6H DKG 6 8DD8: C I@>DC G@< D; @ Z& >K: CI=>HDD8: C I@>DCG@< >I>HD; >BED@6C8 ID8DCH9: GI=: 6FJ: DJH@H7>A>ND; 8J@JB>C 6H>I>H=: H@H7A ;DGBD; 8J@JB>C L=>8 LDJ@7: I6@CJE 7N8: A@>C8JAJ G: J 7AH@9 96I6 :M>HDCI=: L6I: G H@H7>A>ND; 8J@JB>C L=: G K6A: HGG@>G; @B C<B% 4 5 ID C<B% 4 5 Z&@ Z& =6K: 7: :C GEDG19 I=: A@< G@< D; H@H7>A>H@A@ANG@A@ 9 ID I=: 8@H6A@H: G@J: G: D; I=: H6G>G B6I: G@A >: :I=: G 6B D@>D@H DGB>MJG: D; 6B D@>D@H 6C9 8@H I6A@C 8J@JB>C "CI=: J 78=B 96I6 76H: 8J@JB>C >H@H9 6H=6K >G 6%B) D; 6C9 >H@G; G9 ID6H6 @6I H@H7A @9N >96A: DG I6G <: I>G I=: E@H6B 6: B 7@C D; I=: 8: A@I >H669>N H@H7A >CH@K: CIH HJB=6H & ; (:I=6CDA6C9 K: <I 67A: D>A6C9 >C76H8 H@H7A>DCH 7JI >H 8=B >8A@H JCH67A >C76H8 H@H7A>DC69 BDG: H67A >C68>98H@H I>DCH 4 5 9 9>D@>ANI=: G >H>K: 9: C8 I=6I >CEJG: L6I: 8J@JB>C 7DI= 6<<G<6I: H4 5 6C9 86C H@A; 6H@H@6I: ID ;DGB9: 8: G@HIG@JGH 4 5 EDH7ANAB >@>G>H67>ANIDE: @B: 6I: 8: A@H >K: C>HAB >I9 H@H7A>N>CL6I: G I=: EGH: C8: D; 7DK@: 6@JB>C , >C8: A@JAJ G: B: 9>JB 6I 8DD8: C I@>DCH; @B ID Z& A@AN6>H>C>@>@H>G I=: H@H7A>ND; 8J@JB>C >C8: A@JAJ G: 9>JB 6I 8DD8: C I@>DCHJE ID Z& 9J: ID >HGEDG19 HD8=>@B: I@G>7>C9>G L>I= H: G: B 6@JB>C 6I 7DI= =>=6C9 AD 6; ;>C>N7>C9>G H@H4 5 7>C9>G ID , 6A: G>G 7JI CD 8DB EA: I@NEGK: C>@>G I=: 67>AND; 9G<HID; DGB6< <G<6I: H4 5 = JH 8J@JB>C @HAB >@>G 6FJ: DJH@H7A>N ED: CI>6A ID 6<<G<6I: 6C9 ;DGBBJ A>B: G@HIG@JGH 6C9 7>C9>G ID , 6G ?JHI H@B: D; I=: 76G@>H6<6>C>H>HG69N JEI6@: >@D 8: A@H

(C : L6 N; DG8J@JB>C ID : CI: G8: A@>H@B EA@7N9>; JH@C ID L: K: G I=>H@DI: >H>C9: G9 ;DGA@>GBDA 8JAJ@L: ><I 8DB EDJC9HI=6I =6K: 6 =>= 9: <G D; E@H6B E@I: >C7>C9>G J @JB>C =6H6 BDA8JAJ@ L: ><I D; 6 ADCH A@< :CDJ<= ID =>C9: G G69N E@H@> I=GD<= I=: E@H6B B: B 7@C 6C9 >I7>C9HID E@H6B E@I: >@H; JG=: G AB >@>G >H9>; JH@C >@D 8: A@H I J9>: H JI>A@>G; AIDG@H: C8 HEB I@H@DEN6C9 7DI= C@DB6 A6C9 86C8: @HJ8: A@H@>C9: 9 699>D@>A>C ;D@B I>D>C>@D I=: 9>; JH@CD; 8J@JB>C >@D 8: A@H; D@AD >G I66 ID =CJ L>I= :>I=: G 6C 6FJ: DJH@H7A>ND; 8J@JB>C 8J@JB>C 7DJC9 ID CI B6C H: G: B 6@JB>C I , DG8J@JB>C 8DB EAM: 9 >CE=DHE=6I>9NA 8=DAC 8D@>G>G A@>H@B: H4 5 DJG=DJGH; >@J76I>DCL>I= ID CBD@H D; 8J@JB>C E: G@>A@D C8: A@H@H@J@9 >C9>; G>G 8: A@H@> A@B@>DCH; DG8J@JB>C DGCDC 86C8@DJH8: A@H@J@JB>C L6 H8A6 GM A@B: 9 >CI=: 8: A@B: B 7@C 6C9 I=: C8AJ H L=>A; DGI=: 86C8: @HJ 8: A@H L>I= BJ 8= A@>G C8A> 6C9 AHA 8NDE@H@B 8J@JB>C L6 HAD 86I: 9 I=GD<=DJ I=: 8: AA"<C: C: G6A 6 A@>H@B A@E@G 6G@>DCCD; 8JG EAM: 9 L>I= I; D@99: 9 6H>G: 8J@JB>C 6 C8: @HJ8: A@H=69 =>=: G AK>AHD; 8J@JB>C 8DCH: CI L>I= I=: >GA@>G C8A> =>=: G AK>AHD; 8J@JB>C L: G: 6AHD7H: G@9 >CE: GE=>G6A7@D@D BDCDCJ8A6 G8: A@H) & >I@A@> 9; @B E@>CIHL>I= 8=G@>8 AIB E=D8N>8 AJ@B >68DB E6G9 ID) & >I@A@> 9; @B E@>CIH L>I= 8=G@>8 AIB E=D8N>8 AJ@B >64 5 = JH ;DG9>; JH@CD; 8J@JB>C >@D 8: A@H >I LDJ@7 6E E: 6G=6I I=: >G>6A@HIE >C<6>G>G: CIGN>@D I=: 8: A@DJA@7: I=: 6HHD 8>@>DCCD; 8J@JB>C L>I= I=: 8: A@B: B 7@C ;D@AD: 9 7N9>; JH@CDJI D; I=: B: B 7@C ID I=: 8NDE@H@B 6C9 HJ7H: FJ: CI@NAB6A@>@>DCCD I=: C8AJ HL>I= I=: DK@>AJEI6@: 6C9 9>H@G7JI>DCCD; 8J@JB>C L>I= >CI=: 8: A@H: E: C9: CI DCI=: 8: A@NE:

&DG: G8: CI HU9>: H=6K: >@>86I: 9 I=6I CD D@N8J@JB>C 7JI >H B6?@B B: I67DA@>H !: I: I G@>N@D8J@JB>C 6C9 8J@JB>C <A@ 8JG@D: 9: B6N 6AHD688: H@B: A@H7N 6C@I=: GGD I: 68I>K: JEI6@: JH>G I=: DG@>8 6C>@I@>CHEDGIGED@H@E: EI@9: (-) 6HL: A@H=: DG6C@ 6C>@I@>CHEDGIG (- =: H: GDI: H D; 8: A@H6I @: 86C=6C9A 6 L>9: K6G>ND; 8DB EDJC9HD; 9>K: GHBDA 8JAJ@L: ><I 8C9 K6GN@G 9: <G H D; E@H6B E@I: >C7>C9>G DI= I=: (-) 6C9 (- I@>CHEDGIGH=6K: 7: :C L: A@HU9>: 9 6C9 :M>HJ7>FJ>DJH@H>C6 K6G>ND; 8: A@H 4 5 ; K :G6ADG6CH HJB=6HI=: AK: G @9C: N 6C9 A@<=6K: E@>8JAJ@G@>= AK>AHD; I=: H: I@>CHEDGIGH 4 @ 5 "C 6 K: GNAD FJ: CI HU9N >I L6 H 9: BDCHG@ 9 >C>JB6 C: B 7NDG@8@9C: N 8: A@H@>C@H: 8I: 9 ID :MEGH =JB6C (- 6C9 (-) I@>CHEDGIGHI=6I I=: G@ D; 8: A@H6JEI6@: D; 7DI= 8J@JB>C 6C9 8J@JB>C <A@8JG@D: 9: L: G: >@>H 9 8DB E6G9 ID C@I@>CHEDGIG: ME@H@>G 8: A@H 4 5 "C 699>DC >CI=: H@B: HU9N 7DI= 8J@JB>C 6C9 8J@JB>C <A@8JG@D: 9: >G>7>I9 GDIK@H6I>C JEI6@: 7N(-) 6C9 (-) 6C9 >@>H 9 I=: E@H6B 8DD8: C I@>DCD; GDIK@H6I>C JEDC8DB9B>C I@>DC>G@H6C9 9D<H K @9: C8 L6 H6AID EGH: CI: 9 ;DGI=: JEI6@: D; 8J@JB>C H@H@6I: >@D I@>CH: 8I: 9 8: A@H "C6 BDG: G8: CI HU9N=DL :K: G I@>CH: 8I: 9 =>C: H: !6 BHIG (K 6@N ! (8: A@H: ME@H@>G (-) 6C9 (-) I@>CHEDG19 8J@JB>C ! I 6 8DCH: FJ: C8: D; I=: H: BDG: G8: CI HU9>: H I=: :CIN D; 8JG 8JB>C 6HL: A@H>H@B: I67DA@>H >@D 8: A@H>H@A@AN7N IL D B6?@B GDI: H 9>; JH@C 6C9 68I>K: I@>CHEDG I A: 6 GM 68I>K: I@>CHEDG I L>A@7: I=: BDHI; ; 8I>K: L6N; DG8J@JB>C ID <6>C: CIGN>@D I=: 8: A@E@>8J A@G@H; DGAID: G: M@G8: A@A@>8DD8: C I@>DCHD; 8J@JB>C "G@H@B I>K: D; =DL 8J@JB>C <6>@H: CIGN>@D I=: 8: AA>HEGH: C8: >CI=: 8NDH@6C9 A@B@>@G ID I=: C8A> 8A6 GM; 6KDJGI=: IL DB6 ?@B@H@ HD; >@>G@>DCCD; DG8J@JB>C >G>7>DCCD; I=: E=DHE=DGM@>DCCD; I=: ' ü "ü y 8DB

EAM >Cl= : 8NDHIA6C9 >G>7>D>CD; l= : 7>C9>G D; ' ü ID ' H L6 HDJIAS:9 EGKDJHM ;DB 8: A&JAJ G:HU9>:H l= : 8DC8: CIGI>DGH; 8JCB>C l=6l >G>7>I9 l= : 68>K>ND; ' ü 9>9 HD6l 8DC8: CIGI>DGH G6<>G;DB Z & ID Z & L>l= >GJ76l>DCl>B: HG6<>G;DB ID = =>HG6<:GA6< G6< D; 8DC8: CIGI>DGH>=<l 7: GA6 9 ID=DL 8JCB>C<6>G: CIGN>D8: AM>:l= :G7N9>; JH6CDG68>K: JEI6@: l= : A6l: G7: >G 9: E: C9: C l DC=DL L: AWEI6@: l: GCHEDGIGH6G :MEGH-H9 >Cl= : 8: AAS: HJH9 ID 8DC9J8l l= : HU9N H 6 <: C: G6AGJA: JEI6@: l: GCHEDGIGH6G :l= : GCD :MEGH-H9 DGMEGH-H9 6l 6 AD AK: A>C8JA lJG9 8: AAS: H l= : >G: MEGH-H9C =>AN9: E: C9: C l DC l= : 8DC9>DGH JH9 ID 8JAJ G: l= : 8: AM> = >H68l E6N9 A6<AN>D l= : G6HID ID JH EGB6 GN8JAJ GH D; =: E6D8N: H6HDEEDH9 ID 8: AAS: HID 9: H6C 6 BD9: AID EG9>8l l= : =JB6 CAK: GE6>D>G< G; 9G<H4 5 "B EAB: C l6l>DGD; l= : JH D; l= : =JB6 C=: E6D8N: l: GCHEDGIGH6G 8: AAS: l: E >Cl= : 9: H6CD; l= : BD9: AL6 HGJA9 DJl 9J: ID 6BD<H D l= : G9>; G :C8: H; DB =JB6 C=: E6D8N: H l: E 8: AM>: 6>AG ID 9>HE6N(-) (-) l= : DG6C8 68<DC l: GCHEDGIG (- 6C9 l= : H9>B l6JGB=DAl: 8Dl6CH6C<EDA6E: El>9: >CFJ6C>; 67A: AKAH 4 5 = JH l: GCHEDGIGH6G 8: AAS: H: l= : G B6NCD DGDQNE63>6ANM EGHI l= : JEI6@: l: GCHEDGIGH6G >BEA66: 9 >Cl= : 8: AAS: JEI6@: D; 8JCB>C 6C9 l= : G; DG: l= : 8: AAS: JEI6@: D; 8JCB>C >D ID GCH ;DGB9 8: AMB6N7: A6<AN9>; JH6GA>CC6JG : = : >BE68l D; l= >H BD9: D: 8: AACIGN7N8JCB>C DC: H68>K>N>C8: A&JAJ G: 68>K>N86C 7: EG9>8l: 9 6H; DADH H 9>HJH9 EGKDJHM 8JCB>C 6 G6l>K: AN A6< BDA8JA: >HID7>ANAB>I9 >C6C6FJ: DJH: CK6IDB: C l6C9 >H E6l: >C7DJC9 "l: HE G: GC l6A7>C9>G IDE6l: >GLDJAJ GHG8l>H9>; ; JH6C68GDH: 8: AAS: B76C -D G68= ;; 8l>K: : CDJ<= 8DC8: CIG I>DGD; 8JCB>C6l ' ü : l= : G>Q= : 8NDHIDG>Q= : C8AJ HL>l= >C l= : >GJ76l>DCl>B: D; l= : : ME: GB: C l l= : 6EEA: 9 8DC8: CIGI>DGD; 8JG 8JB>C LDJA9 =6K: ID 7: => : CDJ<= >C l= >H6H: >Cl= : JEE: GZ& G6< ID 9G>K 8JCB>C >D l= : 8: AM> = JH l= : 7J>8>G JE D; HJ;> 8>C l FJ6C>H D; 8JCB>C >D l= : 8: AAS: B76C ; DG9>; JH6C>D ID l= : 8: AA6 l>B: 6C9 8DC8: CIGI>DGD: E: C9: C l E68HH 6EE: 6GHID 7: 6 8G l66AAB >B>G HIE ; DG8JCB>C >D HIE: A&JAJ G: 68>K>N = : ED: C l6A ; DG8JCB>C ID J l>A9: l= : EA6B 6: B76C 6H6 6H6 6H6 G6D: G; DGB6>C l6>G>G >D68: AAS 8DC8: CIGI>DGD; 8JCB>C B6N8DCIG 7l: ID l= : AD<A6H>G : ; 8lHD; 8JCB>C>C8: A&JAJ G: J G=: GBDG: l= : 9>; G >G 8DB EDH>DC6C9 HJG68: 6G6 D; l= : EA6B 6: B76C >C9>; GCl 8: AM> B6N8DCIG 7l: =DL BJ 8= 8JCB>C 86C7: >DDEEG 9 >D l= : EA6B 6: B76C 6C9 =DL BJ 8= 8JCB>C l>A6C: G>D8: AMGHJA l >G >C K66NG : ; 868>H ; DG >G>7>G>' ü 9: E: C9: C l 8: AAS: E68HHH = : H: E6B >H66G HJEE6G 7NHK: G6AHU9>: H9: l: G>C>G l= : ; 8lHD; 8JCB>C DC' ü 9: E: C9: C l 8: AAS: E6A>G6l>DC J G 8JB>C E69J8: 9 6 8DC8: CIGI>DGD: E: C9: C l >G>7>DGD; 8: AAS: E6A> : G6l>DC>CHME6C8G6l>886C>C l6 8: AAS: H9: H>C6: 9 6H H) M) 6 E6C 6 E6C !, - 6C9 & u6) 6 6 L>l= : K6W: HD; 6C9 Z & GH68l>K: AN# 5 "C<: C: G6A 8JG 8JB>C >G>7>I9 8: AAS: E6A>G6l>DCBDG: ED: CIAN>l= AD<G>>GJ 76l>DGHl>B: H 6 =GH K6W: HG6<>G; DB ID Z & 4 5 8DB E6G9 ID H>6G G>GJ76l>DGHl>B: H 6 =GH L>: G : l= : G CD ; ; 8l L6 HD7H: GK9 DG K6W: HD; ü Z & 6C9 <G6l: GL: G: D7 H: GK9 = : G; DG: 8: AMNE: 6C9 : MEDHJ: l>B: E6N6 8G l66AGlA: >C8JG 8JB >D H>G>7>DGD; ' ü 9: E: C9: C l 8: AAS: E68HHH 6 E=: C l B: C l C l BDG: 8DC8: C l l>l= l= : 9>; JH6C; 8JCB>C >D l= : 8: AAS: HDE EDH9 ID 68l>K: l: GCHEDGIG 0= >A l= : 68>K>ND; JEI6@: l: GCHEDGIGH>C8JAJ G9 8: AM60C D 7: 8DB EA : AN GA9 DJl l= : >BEA66>DGHLDJA9 7: l=6l 68l>K: JEI6@: D; 8JCB>C >D8: AMLDJA9 G9J8: l= : l: MG68: AAS 8DC8: CIGI>DGD; 8JG 8JB>C GFJ>G ID >G>7>I9 ü "C: 68l >Cl= : EGKDJH8: A&JAJ G: 68 l>K>N96l6 EGH: C l 9 ; DG8JCB>C l= : G: L6 H6 => : K6G67>AND; 8: AA 68l>K>N A>IA ID B6 G @ 68l>K>N ; DG8JCB>C 6l AD: G8DC8: CIGI>DGH >: 6 Z & = >H6N7: AS @ ID l= : MEGH-H9CD; JEI6@: l: GCHEDGIGHDC8: AMA.69>G ID 6 B6 G @ 68l>K>ND; 8JCB>C D6G A6 @; JE I6@: l: GCHEDGIGH6C9 9>; JH6C9DB >C6: 9 8: AWEI6@: A69>G ID AD: G 8: AAS 68l>K>N ; DG8JCB>C H l= : 8: A&JAJ G: 8DC8: CIGI>DGH; 8JG

8JB>C>G6H9 =>:G8: A&8l>K>N; DG8JCB>C EG9DB >C6: 9 9J: ID 69: FJ6l: E: G6: 6l>DGD; 8JCB>C >D l= : 8: A&N9>; JH6C>C699>DGD ID 68l>K: JEI6@: = : ED: C l6A; DG8J A>EA E6l=L6 NH; DG8JCB>C ID <6>C688: HH>D8: AME6K: 9: H6 EA6H7A : MEA6C6>DC; DGI= : D7H: K6 l>DGD; K6G67A: GH6GH>HD; ' ü ID 8JCB>C 6l AD: G8DC8: CIGI>DGH >C8: A&JAJ G:

4. In vivo interaction of curcumin with NF-κB: Animal studies

K9: C8 6AD: M>H; DB 6C66AHU9>: H>G>8D>G l=6l D6A6C9 E6GCl: G69DH>G L>l= 8JCB>C A69HID l= : >G>7>DGD; ' ü 9: E: C 9: C l 8: AAS: G68HHH6C9 >CHB: 86H: H l= D6J<= HU9>: H=6K: 7: : C E: G6GB9 ID H>D L >G>7>DGD; ' ü 9: E: C9: C l E68HHH>C8: A&JAJ lJG: H: HU9>: H8>: 9 67DK l=6l 8DC8: A6 l>l= l= : E6A>G6l>DGD; 86C8: G>C6C66AHID L: K: G 6HL>AA7: 9>8JH6 l= : H: H6C>86C l ; ; 8lH6l ' ü in vivo D8JG6l K: GNAID B: 6HJG9 8DC8: CIGI>DGD; 8JG 8JB>C>CE6H6

(l >H 9:6 (& >H6 8DB BDC 8=>8=DD9 768l: G6A>C: 8l>DC6C9 A69>G 86H D; 8DC9J8l>K: =: 6G>G ADH'D C l NE: 67A: l6 : B DE>AJH >CAI: CO6 ' -! > >H6 B6?D6768l: G6A E6l=D<C ; DG (& D CHH: C l L>l= l= : ; ; 8lHD; 8JCB>C DCB>99A : 6 G E>E: A6A8: AM>C: 8l: 9 L>l= ' -! > : l= : G EG l66 lB : C l D; % B>8: ; DG = 7N>D6E G6DC: 6A ") >C: 8l>DGD; B< @>8JCB>C; DAD: 9 7Ntrans INBE6C>8>D8l A6DCL>l= ' -! > DG66 lB: C l l>l= 8JCB>C B< @<" = 6; l: G ' -! >G>7>I9 ' -! >GJ8: 9 1 % : MEGH-H9C in vivo 4 5 J G 8JB>C HJEEGH: 9 1 % : MEGH-H9C 7N 9>G8l >G>7>DGD; l= : E=DH E=DGM6DCD; l= : ' ü "ü HJ7JC>l6C9 >G>7>DGD; E K6 >GJ8 l>DGD; l= : C: <6l>K: G<J A6DGB>ID<: C68l>K6: 9 E6l: >C6G6H: "C6 G67> BD9: AD; IDM8 H>D8@H6C9DB: - , >GH6A6DCD; ZBD6H D; 8JCB>C >D l= : K6<C6D; G67>HJEE: 8l: 9 6<6>CH l= : A l=6A; ; 8lHD; -, , B: 9>6l: 9 7N>D6K6<C6A69B>C>H6l>DGD; IDM8 H>D8@H6C 9DB: IDMS - , - IDMS 4 5 & 6 CND; l= : K6<C6A: E>E: A6A: C: H l=6l 6G JEG<JA6 9 >CGH6GH: ID-, - 6G @DLC' ü G<JA6 9 <: C: H4 5 Ex vivo 6C6AHHD; K6<C6A l>HJ ; DB G67>HJ6G l: 9 L>l= 8JCB>C H>D L: 9 AD AKAHD; ' ü 8DB E6G9 ID 8DCI DAG67>H6C9 ü CBD6H D; 8JCB>C G B6>G>G = ; DAD >G l66 lB: C l = : H: ; C9>G>H>G6: l=6l AD IDE86A: MEDHJ: D; K6<C6A l>HJ ID 8JG 8JB>C G HJA l9 >CH>C>86C l E6l: 8l>K: ; ; 8lH6<6>CH l= : A l=6A; ; 8lH D; -, , IDMS 6C9 G HJA l9 >CG9J8l>DGD; 8ND@G: E69J8l>DCB: 9>6l: 9 7N' ü B E6N>G; ; B6A: G6H6C9 6 BD9: AD; 8= B D l= : G6N>GJ8: 9 >G: HIC6ABJ 8DH676G>G>GJ8: 9 7N B: l= DIGM6l: & -1 6C9 B: 9> 6l: 9 7N' ü : C: G6l: 9 B: 9>6l DGD; >C6B B6 l>DC l= : >GJ8l>DGD; ' ü GA6 9 8ND@G: H6C9 8= B D @CH L6 H9: l: 8l: 9 JEDCIG6 lB: C l l>l= & - 1 4 5 J CB>C 69B>C>H G9 >Q= : 9>l 6l 6 9DH: D; B< @<96N; DG; DJG96NH>G>7>I9 ' ü 9GK: C 8ND@G: E69J8l>DC6C9 6B: A6G6 9 BJ 8DH6>GJGNDAD >G & - 1 69B>C>H6l>DGD "C % 8 B>8: >C: 8l: 9 L>l= \$A7 H>AA6ECJ BDC6: 7N>D6G6H6A>GH6A6 l>DC; >l: : C 96NH; D6AIG6 lB: C l l>l= 8JCB>C 6l B< @<96NG: HJA l9 >G H6C>86C l 9: 86H: >C l= : E69J8l>DGD; B6 AD>G6A: = 9: 6C9 C>DJH DM9 H L: A&JCB>C l66 lB: C l G9J8: 9 l= : 68l>K>ND; BN: ADE6DM 96H: 6C9 9: 86H 9 ' ü AKAH>C l= : 67H: C8 D; 6 9: 86H: >C768l: G >6A l9 4 5 . H>G>G 6CD G DIDE: 8 BJ G6: BD9: AD; D l6G6C 86C8: G4 5 : B E6N>G 6 l=NB>8 B>8: l= : ; ; 8lHD; D6A8JCB>C HJEE: C9: 9 >C ; H6: H: 9 D A 6l 9DH: HG6<>G; DB ID B< @<L: G: 6H H: H6D DCl= : BD9JA6DCD; ' ü 6C<D<: C8 8ND@G: H 8: AAS: E6A>G6l>DC 6C<D<: C: H6C9 6 ED6DH6 In vitro : ME: G6: C l HJH>G = J B6 C D l6 G6C 86C8: G8: AAS: H6C9 BDC l D G>' ü 68l>K>NL: G: 6AD 8DC9J8l: 9 J CB>C Z & L6 H; DJC9 ID >G>7>I9 >GJ8>7A ' ü 68l>K6>DC>CGH6GH: ID-' ü 6C9 HJEEGH: 9 lJBDG8: A6A>G6l>DC In vivo 9DH: ; C9>G: ME: GB: C l HGK: 6A9 l=6l B< @<8JCB>C 69 B>C>H G9 D6AANDGL D96NH6 H l= : DE>B6 A9DH: C: : 9 9 ID HJEEGH ' ü 6C9 H6C6A l6C9J8: GH 6C9 68l>K6DGDH; l: GCHEDGIGH6C9 68l>K6>DC6C9 9: 86H: 6C<D<: C8 8ND@G: : MEGH-H9C J G=: GBDG: D6A9DH>G; DG 96NH>l= B< @<D; 8JCB>C l >8 E: G96NG:

HJA19 >C6 Đ G9J8I>DCD; B: 6C DKG6C IJBDG<DLI= 8DB E6G9 ID 8DCI DAIL6 HD7H:GK9 H 6 8DCH:FJ:C8: D; ' ü ÖHDA:>C>C G<JA6G 8: AA<DLI= 6C9 EGA>G6I>DC I=: 67>ANID; 8JGB>C ID 7: 6C>E6A>G6I>K: 6C9 E6E6E6I>8 >CE6C8G6I>88: AHAAS:H6C9 ID G: 9J8: I=: <DLI= D; E6C8G6I>8J IBDGH>CB>8: L6 H>K: H>6I: 9 4 5 In vivo, >C; B6A: 6I=NB>8 CJ CJ B>8: Đ L: :@HDA >ÖGK:CDJH "/ 69B>C>H6I>DCD; B< @<D; AEDH6A 8JGB>C I=G: I>B: H E: G L: :@:DGIL DL: :@HGHA19 >C6 HEEGH6C I=: <DLI= D; E6C8G6I>8 8: AAJBDJGH6C9 6 9DL C G<JA6DCCD; ' ü 9: E: C9: CIB6 G@HD; IJ BDG6C>D: C: H H

-6 @C<D: I=: G I=: H: HU9>H>G>86: I=6I 8JGB>C L=: C 69B>C>H I: G9 ID 6CB6AH86C >G>7> I=: 68>K6>DC D; ' ü 9: E: C9: C I E6D8HH in vivo 6C9 8DB E6G6I>K: AN>C8: A&AJJ G: H B: C I>DC9 67DK I=: :; :; 8IHD; 8JGB>C 6I ' ü ;DAAD >G: HMI: B>8 69B>C>H6I>DC6G D7H:GK9 6I AD EASHB6 8DC8: CIGI>DCHD; 8JGB>C =>JH >I>H>BEDG I6CI ID <6>C6 ; JG=: G J C9: GH6C9>G D; I=: GA6DCH>E7: IL : : C I=: EASHB6 AK>AHD; 8JGB>C >H in vivo I6G IB: C I: :; 8IH6C9 =DL I=: H: G: A6 ID 8JGB>C>H6I>DC8: CIGI>DC9: E: C9: C I: :; 8IH6H6C >G>7>DGD; ' ü >C8: A&AJJ G:

5. Pharmacokinetics and tissue and cell distribution of curcumin

=: E=6668D@G:I>8HD; 8JGB>C ;DAAD >G: 7DI= DGA6C9 E6G :C I: GAGDI: H ") 6C9 "/ D; 69B>C>H6I>DC=6K: 7: :C :MI: CHK: AN>C K: H>6I: 9 7DI= >CEG8A>G6A6C6B6 ABD9: AH 6C9 =JB6CH6C9 =6K: 7: <L: A&: H67: 9>CH:K6A@NGK: L H4 5 "C7G: ; ;DAAD >G: DGA 69B>C>H6I>DC I=: EASHB6 AK>AHD; 8JGB>C 6I I6>C9 >C I=: EASHB6 6G K: GNAID 6H6 8DCH:FJ:C8: D; EDD67H6E6C J GB>C>H6I>DC67 H6E6DC>H9J: >HAD HIA7>AN 6C9 I=: B: I67DA8 >GH67>AN D; 8JG 8JB>C 9JG>G 67H6E6DCE68H6I I=: 7GH: 7D9: GB: B 76C L=: :G: :MI: CHK:)=6H "" <AJ8JG96I>DCD; 8JGB>C D8JGH: 9:6I:9 EG B6G>N7N>Q: HIC6A - 6C9. - 4 5 (C 8: 67H679 >D I=: 8>GJA6>DC6C9 >D I=: AK: G6C9 A@ANDE: GI>HJH EASHB6 8JGB>C J C9: G:DH:MI: CHK: E=6H " B: I67DAH B >: 68>DCD; G9J8 I6H: :COIB: HDC6A@C: 7DC9HGHA19>G>C I=: 8DCK: GH6CD; 8JGB>C >D>I! 6HL: AA=: G9J8I>DCD; @IDC: <DJEHD; DGB K69DJH6&D =DAB: I67DA8>H6AD; L=>8 EDH:HHK6GN9: <G HD; 7>DAB>86A68>K >N)A6H6 8JGB>C>H6AHDJ7?>8I:9 ID)=6H "" B: I67DAH B E6G6 G >N <AJ8JG96I>DC7N. - >C I=: AK: G4 5 6C9 6 BJ 8= HB6A&G 8DB EDC: C I D; HJA6I>DC4 Đ 5; DAAD: 9 7N 68>K: I6CHE6GI>D I=: 7AD9 6C9 :M8GI>DC>C I=: JG-C 0=>A 7>DAB>86A6>G8I: I=: <AJ 8JG9: HD; 8JGB>C 86C7: 9: 8DC7Jk6I: 9 IDN>A9 68>K: 8JGB>C K6 I=: 68>DCD; I>HJ 6C9 EASHB6 p <AJ8JG96I>DC4 Đ 5 J GB>C <AJ8JG9: >H=: B6?D8DB EDC: C I D; IDI6AEASHB6 8JGB>C>D>9H 8JG 8JB>C EASHB: I67DA8 H

DBE6G9 ID DGA9D>G: E6GCI: GAGDI: H D; 69B>C>H6I>DCG: HJA19 >C>=>E GASHB6 AK>AHD; 8JGB>C 7: >G D7H:GK9 4 Đ 5 "C6K: CDJH>CJH6DHIU9>HD; AEDH6A 8JGB>C>C9D>H6C9 =JB6CH6A6G9: BDCH6 I=: 67>ANID B6>D6>CHJH6>C9 AK>AHD; 8JGB>C 9JG>G >CJH6C 7J IJEDCI: G6>C8>DCD; >CJH6CI=: EASHB6 AK>AHD; 8JGB>C :6AK: GNGE9AID 6ABDHIJ9: I: 8I67A: L>I= B: 6C GH9: C8 I>B: HD; B>C>C9D>H6C9 Đ B>C>C=JB6CH, >B A6G6I >ÖGK: CDJH 7DAH 9DHI: H D; 8JGB>C E6K9: ;DG H>D6 AK: 9 =>=> EASHB6 8DC8: CIGI>DCHD; 8JGB>C &DG: G8: C I HU9>H=6K: 9: BDC HG6 9 I=6I 8JGB>C >HB: I67DA9: 9 7N G9 7AD9 8: AHA>C6 HEB>: H 9: E: C9: C I B6CC: GL>I= ! 7: >G >9C I>9 6H6 B: I67DA8 4 5 >K: C I=: 67JC96C8 D; G9 7AD9 H I=: G9 7AD9 8: A&: I67DAH B>C69 9>D>CID=: E6>8 B: I67DAH B D; 8JGB>C A@ANBDG>Z I: H I I=: G6E: 9 9: 86H: D; EASHB6 8JGB>C AK>AHD; DAAD >G: >ÖGK: CDJH 9D>G: "C 8DCI6H H68 8JGB>C =6H I=: ED: C I>6AID 688JBJ A6 >C I=: 8: AA B: B 76C G9 7AD9 8: A&B6N6AIDH: GK 6HK: =>AH ID 9>H>Z I: 8JG 8JB>C>D I>HJH >CBJ 8 I=: H6: B6CC: G6H7>C9>G ID EASHB6 ED I: >GHL=>8>G6H I=: HMI: B>8 9>HG7J I>DCD; 9G<H

") 9D>G: L>I= 8JGB>C 86C GHJA19>C>=>G EASHB6 AK>AHD; 8JG 8JB>C DKG 6 HIB: L=6I AD<G E: G996H6 8DCH:FJ:C8: D; I=: A6@D;

;>GHE6HB: I67DAH B 6C9 HJH6>C9 67H6E6DC; DB I=: E: GHD: JB !D L: K: G 7DI= :C I: G66C9 E6GCI: GAGDI: H D; 69B>C>H6I>DCGHJA19>C 8=6C: H>C I=: E: G: A: D; 8JGB>C B: I67DA8>H E6G8JA6G I=:)=6H "" B: I67DA8>H L=: :G ;DG: M6B EA =>=>GAK>AHD; 8JGB>C <AJ8JG9: 6G D7H:GK9 ;DAAD >G: DGA 69B>C>H6I>DC E6G8JA6G >C G9: C I H 8DB E6G9 ID =JB6CH

"C8DCI6H ID 8JGB>C>H6I>DC6 E=6668D@G:I>8H I=: I>HJ 9>HG 7J I>DCD; 8JGB>C=6H7: :C AHHL: AA>K: H>6I: 9 >CEG8A>G6A6C6B6 A BD9: AH "C G6H 7DAH>ÖGK: CDJH69B>C>H6I>DCD; B< @<D; :I=: G 8JGB>C D8JGB>C 6H6 C6CE63>8A EGE66DCGHJA19 >C9: I: 8I67A: 6K6C< I>HJH AK>AHD; 8JGB>C DKG B>C >C AK: G C<< =: 6G C<< H6A: C C<< A<C C<< @9 C: N C<< 6C9 76C C<< L>I= I=: C6CE63>8A EGE6G6 I>DCD; 8JGB>C 9: AK>G>G BDG: 8JGB>C>D I>HJH E6G8JA6G>C I=: A<C<6C9 I=: H6A: C ;DA96C9 ;DA9BDG: GHE8I>K: AN 8DB E6G9 ID 8JGB>C DC>HDL C 4 5 ID L: K: G I=: I>HJ =6A; AK: H6C9 B: 6C GH9: C8 I>B: HL: G: K: GN>D6G6C>G; DB ID B>C 6C9 Đ B>C GHE8I>K: AN; >B A6G6I >CB>8: 69B>C>H6I>DCD; B< @<D; 8JGB>C 7N7DAH6>AK>C>C>8I>DCGHJA19 >C9: I: 8I67A: 6K6C< 8JGB>C AK>AHD K G B>C>EASHB6 Z< B% Z& AK: G C<< I>HJ @9C: N C<< I>HJ 6C9 76C C<< I>H HJ L>I= EASHB6 6C9 I>HJ =6A; AK: HD; 6C9 B>C GHE8I>K: AN! 5 "C G6H I=: G: 9>; GC I ;D&J A6DCHD; 8JGB>C L: G: :K6A6I: 9 ;DGI=: >G67>AN ID 9>HG 7J I: 8JGB>C>D I=: 76C AEDHD B6A 8JGB>C EDAIB: G8 C6CE63>8A 8JGB>C 6C9 EDAIB8>8<AN 8DA8 68>98DEDAIB: G)% 8JGB>C; DAAD >G: >ÖGK: CDJH69B>C>H I6I>DC4 5 (; I=: I=: G: ;D&J A6DCH I=: C6CE63>8A ;D&J A6 I>DC B< @<E6G9 8: 9 EASHB6 AK>AHD; 6C9 C< B% 6I =G 6C9 =GH; DAAD >G: 69B>C>H6I>DC G6>C HIB AK>AHD; 8JGB>C 6I =GEDHI>C>8I>DCL: G: C<< I>HJ 6C9 >G6H 9 ID C<< I>HJ 6I =GEDHI>C>8I>DC "C 8DCI6H I=: 69B>C>H6I>DCD; AEDH6A 8JG 8JB>C GHJA19 >EASHB6 AK>AHD; 6C9 C< B% 6I =G6C9 =GH ;DAAD >G: 69B>C>H6I>DC GHE8I>K: AN G6>C HIB AK>AHD: G: 6C9 C<< D; L: I I>HJ >G6H>G HA<IAN6I =GEDHI>C>8I>DC9: HEI 6 =J<: 9D6E>EASHB6 AK>AHD ; K6A>G: GHI>G ED>CH 86C 7: B69: ;DB I=: H D7H:GK9>DCH >GH9 9: HEI 6 I=: G: 7: >G 6C9 ;DA9=>=>GEASHB6 8JGB>C AK>AHD 9: 7NI=: C6CE63>8A ;D&J A6DCH 8DB E6G9 ID I=: AEDH6A D&J A6DCCD; 8JGB>C 6I =G 6C9 =GEDHI>C>8I>DC 76C HIB AK>AHD; 8JGB>C L: G: DCAN 6C9 =>=>G; DAAD >G: 69B>C>H6I>DCD; I=: C6CE63>8A ;D&J A6 I>DCH: k<: H6 I=6I :A K6>G EASHB6 AK>AHD; 8JGB>C 6B6N CD 8DC I6>Z I: I=6I BJ 8= ID <G6 I: GI>HJ AK>AHD; 8JGB>C FJ>I EDH7AN 9J: ID AB >6I>DCH; DG 8JGB>C E: C: I6I>G I=: 7AD9 76C 76G>G >K: C I=: D7H:GK9>DC I=6I I=: I>HJ AK>AHD; 8JGB>C GHI: BD9: HIAN ID BD9: G6I: AN6I =GH8DB E6G9 ID =GEDHI>C>8I>DC ;DG7DI= ;D&J A6DCH >I>HA@AN=6I I=: A<C<D: I: I>HJ :MEDH:G: ID 8>GJA6>G 8JG 8JB>C>C I=: 7AD9 =6H6C >BED6CI >CAI: C8: DCI=: 9>HG7J I>DCD; 8JGB>C>D I>HJH *J >I 8A6G9 9: HEI I=: G6E: A>B>C6>DCD; 8JGB>C; DB I=: EASHB6 >I86CH6A9>H>G>Z I: >D I>HJH I=: AD<G I=: :MEDH:G: ID 8JGB>C I=: <G6 I: G I=: I>HJ 9>HG7J I>DCD; 8JG 8JB>C

&DG::ADFJ: C I HU9>H: K6A6I>G 6C9 GA6>G I=: E=6668D@G:I>8H D; 8JGB>C ID >H>HJ 9>HG7J I>DCL: G: 86G9 DJ I: B EADN>G >ÖG K: CDJH AN>CJ H9 %E6DJG8 6 AEDH6A C6CE63>8A EGE6G6DC 4 5 6C9 =6K: H=9 699>D6GA=I DCI=: GA6DCH>E7: IL : : C I>H HJ AK>AHD; 8JGB>C 6C9 I=: I>B: D: ;MEDH:G: ID 8>GJA6>G AK>AHD; 8JGB>C>C I=: 7AD9 %E6DJG8 L6H>ÖGK: CDJH AN>CJ H9 >D I: 6 <A 9D>H6I 9DHI>D; B< @<=>G; DG = ID6A9DH: B< @<6C9 B< E: G@<DG = ID6A9DH: B< @<"C: I=: G6H: B>C; DA AD >G>CJH6C I>HJH L: G: =6K: H I9 6C9 6C6A9D9; DGI=: >G8JGB>C 8DCI: C I>C6 B: 9>6 8DCI6>G>G E=DHE=DG868>9 ID H67>A9: I>HJ 8JG 8JB>C &6MBJ B EASHB6 8DC8: CIGI>DCH6C9 EASHB6 :MEDH:G: ID 8JG 8JB>C L: G: C< B% 6C9 C<=>GB %; DGI=: = D; >CJH6C6C9 C< B% 6C9 C<=>GB %; DGI=: = D; >CJH6C DG>I=: G>CJH6C I=: A<C< I=: I>HJ L>I= I=: =>=>H I ;G8>DCD; IDI6AHMI: B>8 7AD9

I=: G6E: 9 9: 86H: D; EASHB6 8JGB>C AK>AHD; DAAD >G: >ÖGK: CDJH 9D>G: "C 8DCI6H H68 8JGB>C =6H I=: ED: C I>6AID 688JBJ A6 >C I=: 8: AA B: B 76C G9 7AD9 8: A&B6N6AIDH: GK 6HK: =>AH ID 9>H>Z I: 8JG 8JB>C>D I>HJH >CBJ 8 I=: H6: B6CC: G6H7>C9>G ID EASHB6 ED I: >GHL=>8>G6H I=: HMI: B>8 9>HG7J I>DCD; 9G<H") 9D>G: L>I= 8JGB>C 86C GHJA19>C>=>G EASHB6 AK>AHD; 8JG 8JB>C DKG 6 HIB: L=6I AD<G E: G996H6 8DCH:FJ:C8: D; I=: A6@D;

;ADL 6C9 6 = < :MEGHHCDC; JEI6@:IGCHEEDGIGH 4 5 8DCI6>C9 I=:
 = < < HI AK'AND; 8JCB>C C < < ;D'AD: 9 7NI=: AK:G C<
 < ;DG=: = D; >CJHDC 0= 6I L6 HE6G8JA6N>C: GH>G: L6 HI=6I 9:
 HEI I=: AD: G6EE6GCI :MEDHJG:ID 8JCB>C9JG>G I=: =GH; >CJ
 HDC I>HJ AK'AND; 8JCB>C: L: G: < < < G>C: C.G6A6BDG>H BDHII>H
 HJH 7JI BDHICD67AN7N ;DA9 C< < 6C9 ;DA9 C<
 < >CI=: A.C< 6C9 AK:G GHEB1K:AN =: :H: 9:;; GC8:HL: G: :K:C
 <G6I: GL=: C DC 8DCH9:GHI=: I>HJ E6G>DC8D; ;>8>CIH;DGI=: A.C<
 6C9 AK:GL=: >8 ;DGI=: = D; >CJHDC: L: 6C9 6C9 ;DGI=:
 = D; >CJHDC: L: 6C9 GHEB1K:AN>HJH AK'AND; !
 6A=DJ< AD: GI=6C; DG8JCB>C 9>HEAN9 6 HB >A6E6I: GQD 8JG
 8JB>C>I= GHEB1 ID I=: H>D6C9 AD<G>CJHDCI>B: H; DG8JCB>C
 6C9 8DC>GB9 I=: :CIGND; 8JCB>C>D I=: 8: AMB6 @& JE I=: I>HJ
 "I 86CI=JH7: 8DC8A9:9 ;DB I=:H: 96I6 I=6I 8DCH: CIL>I= I=: HU9
 >:HD; = >J: I 6A 4 5 AD<GI>HJ :MEDHJG:ID 8JCB>G AK'AND; 8JG
 8JB>C B6N GHAJ>C> < < < G I>HJ AK'AND; 8JCB>C >C6 B6CC: G9>H
 E6ED>DGI: ID I=: EASHB6 AK'AND; 8JCB>C

-=: 9HG7J1>DCD; 8JCB>C>CI=: ;DGBD; %EDBJG8 =6H6AD7: :C
 >K: H>6I: 9 >C6 K6G>ND; ;GH=AN>BA6: 9 DGBDEGH:K9 7JI K67A:
 7AD9 8: AANE: H>G9>G) & 6C9 G9 7AD9 8: AM; DB 9D< 6C9 =J
 B6C) & ;DB =: 6A=N 6C9 8=GID: 8 AB E=D8N>8 AJ@B >6E6>CIH
 AB E=D8N: H6C9 BJ A>EA BN: ADB6 8: AMAS: H; D'AD >G >GJ76I>DC
 L>I= 8JCB>C 6I 8DC8: CIGI>DCH7: IL :: C 6C9 Z& >CI=: ;DGBD;
 %EDBJG8 ;DGJE ID B>C>CI=: EGHC8: D; EASHB6 HJEA
 B: CI: 9 B: 9>JB 4 5 -=: GHJAH; I=: H: HU9>H76H9 DCI=: >C68: A
 A.A68DC: GHDCD; 8JCB>CID-! 9: BDCHG6 9 6 CD67AN> < < G9>H
 IG7J1>DCD; 8JCB>C >D 86C8: DJH8: AM8DB E6G9 ID CD6B6A8: AM
 8DCH: CIL>I= 6 D ;DA9 < < < G JEI6@: D; 8JCB>C >C6 7G6 HI86C8: G
 8: AAG: 8DB E6G9 IDL>A9INE: 8: AM4 5 GIA: ;DGJEI6@: IGCHEEDGIGH
 >CI=: 9HG7J1>DCD; 8JCB>C >D CD6B6A) & =6H7: :C EGEDH9 >C
 I=: A6G6IJG: 4 5 JEI6@: IGCHEEDGIGH7: >G 6HH: H9 6HI6G: IH; DGI=:
 9: K: AEB: CI D; 6C>86C8G 6<CIH 4 5 -=: JH >I LDJA9 6EE: 6GI=6I
 EASHB6 8JCB>C >H6K>67A: ;DG9; JHDCB: 9>6I: 9 6C9 68K: JEI6@:
 >D 7AD9 8: AM6HL: A6HI>HJH

>K: CI=: B: I67DA8>C6I7>A>ND; 8JCB>C >HG69 GBDK6A; DB
 I=: EASHB6 6C9 I=: AD HJH6>C9 EASHB68DC8: CIGI>DCH; 8JCB>C 6
 CJB 7: GD; GH66E= <DJEH=6K: FJ: HI>DC9 L=: I=: GI=: I=: G6E: JI>8
 7: C: ;>HD; 8JCB>C6G 9: GK: 9: DB 8JCB>C>DIB: I67DA6: H4 5
 BDG: HE8>86AML>I= I=: 8DC: GHDCD; 8JCB>C <A8JGID9: ID 8JG
 8JB>C 6H8JCB>C <A8JGID9: >HEGH: CI >C8DCH9: G67AN> < < G 8DC
 8: CIGI>DCH 8DB E6G9 ID 8JCB>C >CI=: EASHB6 G8: CI HU9N
 9: BDCHG6 9 I=6I 8JCB>C <A8JGID9: L=: :C 69B>C>H 9 7NI=: "/
 GDI: ID G6HGHAJ9 >CH>C>86CI EASHB6 8DC8: CIGI>DCH; 8JCB>C
 4 5 A@ANK6 >C 68>DC L>I= I>HJ 6C9 EASHB6 p <A8JGID9>GH
 4 5 "CI=: H6: HU9N 69B>C>H6I>DCD; 8JCB>C <A8JGID9: >C
 IGK: CDIHAND B>8: L>I= 8DAD 866>CDB6 MCD: GE=HGHAJ9 >C6 H6
 C>86CI IG6IB: CI :: ; 8I =: JH in vivo 8JCB>C <A8JGID9: A@AN
 H: GK 6H6C >BED6CI GH: GK>D; 8JCB>C ;DGI>HJ JEI6@: 6H=6H
 7: :C EGEDH9 7N06 C<I: 6A 4 5 H 8JCB>C <A8JGID9: H>DJA97:
 BDG: HAJ7A I=6C 8JCB>C 6C9 A>HE6I: >C7DJC9 H>B>AGID I=: 9>H
 I>C8>DC7: IL :: C: HI69>DA6C9 :HI69>Dp <A8JGID9 4 5 96I6 ;DG
 8JCB>C p <A8JGID9 6G CD 6K6>67A: >CI=: A6G6IJG: >I H>DJA9
 6AD7: 7: II: G9>HG>ZJ: 9 7: IL :: C I=: EASHB6 6C9 >C: GH>6A; AJ9
 =: JH 8JCB>C <A8JGID9: LDJA9 A@AN: BDG: 6K6>67A: ;DG9>G8I
 JEI6@: >D 8: AM7N68K: IGCHEEDGII=6C < < < ANEASHB6 E6I: >C7DJC9
 8JCB>C J CB>C <A8JGID9: LDJA9 6ADH: GK 6 HDG: D; >C: GH>
 I>6A8JCB>C ;D'AD >G 8DC: GHDCID 8JCB>C 7N>C: GH>6A; AJ9 p
 <A8JGID9>GH 68K>N; DG68K: IGCHEEDGJEI6@: >D 8: AM "CHJEE6I
 D; I=>HE6 >H 6 G8: CI HU9N 9: BDCHG6 9 I=6I I=: 9HG7J1>DCD;
 9DMG7>8>C >D 7DC6=>A866>CDB6 I>HJ L6 H; DJC9 ID 7: 8DCH9: G
 67AN>G6I: GL=: C 69B>C>H 9 6HI=: <A8JGID9: 9J: ID 8DC: GHDCD;
 9DMG7>8>C <A8JGID9: ID 9DMG7>8>C 7N I=: 68>DCD; I>HJ <A
 8JGID9>6H: H4 5 86C8: DJHI>HJH 8DCI6>G>G 6C>G6H9 68K>ND;
 p <A8JGID9>GH 8DB E6G9 ID CD6B6A I>HJ 4 5

"CH.B B6GN16@&G 6AI=: 6;DGB: CI>DC9 D7H:K6>DG>D 8DCH9
 :G6I>DC DC 8DJ/A9 EG9>8I I=6I 8DB E6G9 ID 8: A&AJJG: HU9>:H I=:
 67>AN D; 8JCB>C ID <G>C688: HHD I=: 8: AM in vivo LDJA9 7: H.E: G6G
 76H9 DC I=: <G6I: GE6: C8ND; JEI6@: IGCHEEDGIGH>CL= DA I>HJH
 6C9 I=: EGHC8: D; I=: 7: II: G9>HG>ZJ: 9 8JCB>C <A8JGID9: >C
 >C: GH>6A; AJ9 J CB>C <A8JGID9: 8DJ/A9 :>I=: G 7: 9>G8IAN6CH
 EDG9 >D I=: 8: AM 6C9 8DC: G19 >D 8JCB>C 7N >D68: AAJG6p
 <A8JGID9>GH DG 8DC: G19 ID 8JCB>C :MIG8: AAJG6 7N p
 <A8JGID9>GH ;DG: ;: 8I: K: JEI6@: IGCHEEDGI>D 8: AM =: JH G A6>G
 I=: IG6IB: CI :: ; 8IHD; 8JCB>C ID >HEASHB6 AK'AND: B: B>A.69
 >G: L=: C 8DB E6G>G EASHB6 AK'AND; 8JCB>C ID I=: 8: A&AJJG: 8DC
 8: CIGI>DCH; 8JCB>C GFJ>C ID 68=>K: 68K>N6I' ü 'D C: I=:
 AHH>I>H>BED6CI ID 6HH: HHH.6 6 G A6>DCH=>EID 8DC>GB I=: G A
 K6C8 D; ' ü 6H6 I6G: I ;DG8JCB>C in vivo

6. Relationship between plasma levels of curcumin and treatment response in preclinical animal studies

6 I6 ;DB 8: A&AJJG: 6C9 in vivo HU9>:H=6K: GK: 6A9 6 CJB 7: GD;
 E6EG>H; DG8JCB>C I=6I B6N=6K: 6 9>G8I 7: 6G>DCI=: GA6DC
 H>E7: IL :: C>HE=6668D@G: I>H6C9 in vivo :: ;>88N6H6C>G>7>DGD;
 ' ü =: H >G9: I=: ED: CI>6A>BE68IH D; I>HJ E: GJHDC I=:
 A.C< D; :MEDHJG: D; I>HJH 6C9 8: AMID 8JCB>C 6 GA: ;DG8JCB>C
 <A8JGID9: 6C9 I=: >BE68I D; 7DI= E6HK: 6C9 68K: JEI6@: IGCHEEDGI
 ;DG>G>G 688: HH>D I=: 8: AAD C I=: AHH>IGB6>GID7: :HI67AH>9
 L=: I=: G6 G A6>DCH=>EM>HH7: IL :: CEASHB6 AK'AND; 8JCB>C6C9 >H
 IG6IB: CI :: ; 8IH B: 9>6I: 9 EG>E6AM DG>CE6GI9J: ID >G>7>D>DCD;
 ' ü >CEG8A>G6ABD9: AHD; 9>H6 H: L>I= I=: 86K: 6I I=6I EASHB6 AK
 :AH D; 8JCB>C G; A8I I=: IDI6A EASHB6 AK: A D; 8JCB>C 6C9 >H
 B: I67DA6: H DGI=>HM: G6H: 86C8: 6C9 >C6B B6 IDGN>H6 H: EG8A C
 >86ABD9: AH>CIG9: CIH=6K: 7: :C 8>DCH: ID BDCDGI=: IG6IB: CI ::
 ; 8IHD; 8JCB>C 6H>G>7>D>DCD; ' ü =6H7: :C >BEA66: 9 6H6C>B
 ED6CI B: 9>6IDG>C86C8: 6C9 >C6B B6 IDGN>H6 H: *J >I 8A6 GW
 I=: G 6I C JB 7: GD; DI=: GEEDH9 >D68: AAJG6G: IH; DG8JCB>C
 I=6I B6NEAN6 GA: >C86C8: 6C9 >C6B B6 IDGN>H6 H: =DL :K: G I=:
 >G>6A: K: CI ;DG6AI=: H I6G: IH>H=: JEI6@: D; 8JCB>C 7N I>HJH
 6C9 8JCB>C>DHCIGN>D I=: 8: AA

BDG: G8: CI GK>L 7N-DB: =: I 6A 4 5 H.B B6G9>HI=: IG6I
 B: CI :: ; 8IHD; 8JCB>C >C6 CJB 7: GD; EG8A>G6A6C>B6 ABD9: AHD;
 86C8: GI=6I >KDAK I=: >BEA66I>DCD; IJBDJG8: AM>: BDJH M: CD
 <GE= BD9: AH 6C9 L=: G 8: A&AJJG: HU9>:H=6K: >G>86: 9 >G>7>D>DC
 D; ' ü 6HI=: B6>DB: 8=6C>HB 9: 9>6I>G IG6IB: CI =: :H >G9:
 E6H6I: 8D>D6I6A 7G6 HI6C9 7G>C 86C8: G N K>GJ: D; >H>G>7>D>DC
 D; ' ü 6C9 G9J8I>DCD; 8ND@G: ;DG6I>DC 8JCB>C =6H6AD7: :C
 H>DLCID7: ;: ; 8I: K: >C6 CJB 7: GD; EG8A>G6ABD9: AHD; >C6B B6 I>DC
 D; L=: >8 >G9: G>J B6ID>96G>G>H 6H=B6 8D>H>H E6C8G6I>H K6H
 8JA6>C6B B6 I>DC6C9 G.C6AE: GJHDC>C7JGN0=>A I=: G 6G B6 CN
 :M6EAD; 8JCB>C>DHCIG6IB: CI :: ; 8IH>CEG8A>G6ABD9: AHD; 86C
 8: G6C9 >C6B B6 I>DC G: 6I: K: AN; L D: I=: H: HU9>:H=6K: HBJ A6C:
 DJH>BDCD>DG9 EASHB6 8DC8: CIGI>DCH; 8JCB>C H 6 8DCH: FJ: C8:
 :K6AI6I>G I=: GA6>DCH=>E7: IL :: C I=: EASHB6 8DC8: CIGI>DCH; 8JG
 8JB>C 6C9 >HIG6IB: CI :: ; 8IH>C6AEG8A>G6A9>H6 H: BD9: AH 6H
 HHH9 L6 HCD EDH7A ,I J9>:H8=668: G>G>G I=: EASHB6 E=6668D@>
 C: I>H D; 8JCB>C EGE6G9 6HE L 9: G>C6FJ: DJH DGCD 6FJ: DJH
 B: 9>JB 6C9 69B>C>H 9 7NI=: GDI: H JH9 >CI=: :K6AI6I>DCD; 8JG
 8JB>C>DHCIG6IB: CI ED: CI>6A>CEG8A>G6ABD9: AH C6B: AN: CI: G6 >C
 8AHD>C>C9>I 6C9 D6A9D>G 6C9 E63CI: G6GDI: H >CIGEGDC: 6A
 6C9 >D6K: CDIH 9D: I>H4 D 5 K: G6< EASHB6 8DC8: C
 IGI>DCH; 8JCB>C 6K L: G: D76>C9 ;DB I=: H: HU9>:H (G6A9DH
 >G>D; 6 B< @>D: D; 8JCB>C>CB>8: GHAJ9 >C6 6K; DG8JG
 8JB>C D; C< B%DKG6 = E: G994 5 6 K6AJ HB >AGDI I=: 6K D;
 C< B%DKG6 = E: G99 D7H: GK9 >DCD DI=: GHU9N 4 5 (G6A
 8DCH: BEI>DCD; 8JCB>C >CI=: 9>I 6I 6 8DC8: CIGI>DCD; L L
 GHAJ9 >C6 6K; DG8JCB>C D; C< B%4 5 ") 9D>G 6 B< @>
 9D: D; 8JCB>C >CB>8: GHAJ9 >C6 6K; DG8JCB>C D; C< B%

DKG6 =E:G994 5 ,J 8=>CDB6I>DCL6HUH ;JAIDECK9: 6C:HI> B6I: I=: ESHB6 AK:AH; 8JGB>C6I16>C9 >CEG8A>G86A9>H6 H: BD9 :AH>CGA6>DCID >HIG6IB: CI ; ; 8IH

"CA#=#I;I=: 9#;>8JAND; JH>E ESHB6 8DC8: CIGI>DGH; 8JGB>C ID GA6 ID >HIG6IB: CI ; ; 8IH>CEG8A>G86A9>H6 H: BD9:AH I=: 9DH: D; 8JGB>C69B>C>H G9 L6 HG:A6 9 ID >HIG6IB: CI ; ; 8I =: IG6 I B: CI :C9ED>DH JH9 ;DG8DB E6GHID L: G: 76H:9 DC:HI67AH#9 :C9 ED>DH;DG86C8: G>: IJBDJGKDAJB: 6C<:D<: C:HH CJB 7: GD; B: I6H I6H:H 6C9 >C6B B6IDGN9>H6 H: 9:<G D; >C6B B6I>DC I>HH ESHB6 8#B D 8ND@G: AKAH =: 8DB E6G>D>H6G H>DL C7: AD ;DG EG8A>G86A86C8: GBD9:AH>C-67A ;DG:CI: G6 9>I 6NHJEEAB: C6 I>DCL>I= 8JGB>C6C9 ;M:9 DGA9DH:HD; 8JGB>C6C9 -67A ;DG E6GC: G6") "/ 6C9 HJ78JI6C:DJH GDI:H D; 69B>C>HIGI>DCD; 8JG 8JB>C DG>C6B B6IDGN9>H6 H: EG8A>G86ABD9:AH I=: 8DB E6GHID;DG 7DI=: CI: G66C9 E6GC: G6GDI:H D; 69B>C>HIGI>DC6G EGH:CI:9 >C -67A

A:6GM ;DB 6 GK>L D;I=: 96I6 EGH:CI:9 >C-67AH 6C9 8JG 8JB>C69B>C>H G9 7NK6GDJHGDI:H:>I=:GGHJA19 D9>9 CD GHJA>C

Table 2

DB E6GHID D; D H: L>I= -G:6IB: CI ; ; 8I ;DG J GB>C D AAD >G C: G6 9 B>C>HIGI>DC>C)G: 8A>G86A C >B6 A&D9:AH; 6 C8: G

Table with 4 columns: J G8B >C, -J BDJG&D9: A %C4= D, -G:6IB :CI ; ; 8I, +: ; G:C8. Row 1: D H: (K:G ID JGH)

Table with 4 columns: J G8B >C9 B>C>HIG9 >CI=: >I, L L, L L, L L, L L, L L, L L. Row 1: L L)GDH6I: 86G8DB6 >CB>8: L: :@H

Table with 4 columns: J G8B >C9 B>C>HIG9 (G6AN, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<. Row 1: B< @< (K 6G6C 86G8DB6 96>N 96NHB>8:)

ú : 8G6H:

Table 3

DB E6GHID D; D H: L>I= -G:6IB: CI ; ; 8I ;DG J GB>C D AAD >G)6 GC: G6 9 B>C>HIGI>DC>C)G: 8A>G86A C >B6 A&D9:AH; 6 C8: G

Table with 4 columns: J G8B >C D H: (K:G ID JGH), -J BDJG&D9: A %C4= D, -G:6IB :CI ; ; 8I, +: ; G:C8. Row 1: -G:6IB :CI 6C9 ,E:8>H

Table with 4 columns: J G8B >C9 B>C>HIG9 ") B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<, B< @<. Row 1: B< @<)6 C8G6I>886G8DB6 I=G: I>B: H6 L: :@;DG 96NHB>8: KDA.B: ú -J BDJG 4 5

ú : 8G6H:

6 IG6IB: CI ; ; 8I 9: E:C9>G DCI=: 9DH: D; 8JGB>C69B>C>H G9 =->H>C: GHI>G D7H>G6>DCL6H>A>HIGI:9 7N EADII>C<I=: 96I6 EG H:CI:9 >C-67AH 6C9 6HI=: 9DH: D; 8JGB>C>K:GHJI=: IG6IB: CI ; ; 8IHE:G8:CI:9 8G6H:D; :C9ED>C ;DGBDC>DG>E<G>HHD>C; 86C 8:G =: GHJAH6G EGH:CI:9 ;DG:CI: G669B>C>HIGI>DC>C><< 6C9 E6GC: G669B>C>HIGI>DC>C><< "/ 9DH>G 96I6 4 56C9 HJ78JI6 C:DJH#>BE6Q: 9 8JGB>C4 5 L: G: CD >G8A9:9 >CI=>HDB E6G HI> DG>C6B B6IDGN9>H6 H: BD9:AH CD<G6E>86A6G&AHHD; I=: 96I6 L6H B69: 6C9 I=: IG6IB: CI ; ; 8IH D; 8JGB>C6 I I=: :HI>B6I: 9 ESHB6 8DC8: CIGI>DGH L: G: GK>L :9 >G: E:C9: CI D; L=: I=: G I=: GDI: D; 69B>C>HIGI>DCL6 HD(GADG)

DGEG8A>G86A86C8: GBD9:AH6C9 7DI=: D6A6C9 >CGE>GDC:6A GDI:H D; 69B>C>HIGI>DC I=:G L6H6 G6HID67A: GA6>DCH>E7: IL : C >CGE>H>G 9DH: 6C9 6 <G6I: GIG6IB: CI ; ; 8I 6 H:9 DCE=6G68D@> C:I>8 96I6 GEDG19 EGK>DJH# 6 G6< D; 6K 8DC8: CIGI>DGH L6H:HI> B6I: 9 ;DGI=: K6GDJHGDI:H D; 69B>C>HIGI>DC76H:9 DCI=: 9DH: D; 8JG 8JB>C69B>C>H G9 8DB E6G9 ID I=: 9DH: 6I L=>8 I=: 6K L6H9 I: G B>C:9 ;DG8JGB>C =-JH ;DG8JGB>C >CI=: 9>I 6I 8DC8: CIGI>DGH G6<>G ;DB ID L L 9DH:9 D6AN6I 9DH:HD; D B< @<= 6C9 9DH:9 ") 6I 9DH:HD; D B< @<I=: :HI>B6I: 9 6K G6<H LDJ#

Table 4

DBE6GHID; D H: L>I= -G:6IB: CI ; ; 8I ;DG J (BJB>C>C)G: 8A G86A C -B6 A &D9: AHD; "C;A6B B6 I>DC

J G8B >C -G:6IB :CI +: <B: C	"C;A6B B6 I>DC &D9: A %C<= D; -G:6IB :CI 6C9 .E:8>H	-G:6IB :CI ; ; 8I	+ : ; G:C8
B< @< >O6EG>DC6A	J)6 C8G6I>HHS<A: 9DH: DKG6 =G E:G99 G6	"% ú -' ýú 8 G68>K: E@t>Qú 6C9 E6C8G6I>8 >C6B B6 I>DCú 7N 6C9 GHEB I>K:AN	4 5
B< @<D6A	GI=G>H 96>N I=G: L: :@H G6H	ú GI=G>8 H@G ú ; G.B "% p ú ; G.B -' ý 6C9 ú GI=G>8	4 5
B< @<D6A	GI=G>H :K:GN DI: G96N;DGIL D L: :@H B>8:	>@: M6C9 >@>: C8 GHEB I>K:AN 6C9 ú "% p 6C9 ' ý AK:AHGHEB I>K:AN ú GDC=>D@A@<6<:	4 5
B< @<D6A	J)AEDG@N >C6B B6 I>DC 96>N 6 NHB>8:	ú DDC=>D@A@<6<: >C6B B6 I>DCN: A@DJCIH ú -' ý B: HHC<: G G7DCJ8A>8 68>9:MEGH@C ú DHS@=>A>CAG@<DC	4 5
Đ B< @< D6A	J)AEDG@N >C6B B6 I>DC 96>N 96NHB>8:	Đ ú >GL6NGHH6C8:	4 5
B< @<D6A	/6 H8A6G >C6B B6 I>DC 96>N 6 NHB>8:	6C9 ú ;DG"% p 6C9 "% GHEB I>K:AN ú &) ú &6IG-M B: I6A@EEI>96H:	4 5
B< @< >O6EG>DC6A	+ : C6A >C6B B6 I>DC 96>N 6 NHG@H	ú G:6I>C<: 8A6 G@8 ú H:G.B AK:AHD; -' ý	4 5

ú : 8G6H:

7: Đ C< B% Đ C< B% 6C9 Đ C< B% GHEB I>K:AN== :
G@< D; :HI>B6I: 9 6K ;DG8J@JB>C;DG:A>8>@< 6 I=:G6E:JI>8 GH@GH:
JEDC:>I=:GD@GADG) 69B>C>H@I>DC8A6 GNDKGA@E9 ;DG:6 8=9D>@<
GDI: D CHH: CI L>I= I=>H7H:K@<DCL6 H6 HB >A@G@< D;IG6IB: CI
; ; 8IHD7H:GK9 ;DG8J@JB>C;DG:6 8=9DH: GDI: D I=:DGI=: D@A6C9
>O6EG>DC:6A9D>@< GDI:H I=: K@G67>AND; I=: IG6IB: CI GH@GH:
ID 8J@JB>C 9: 8G6H:9 L>I= >@G6 H>@< 9DH: HB >A@<ID D7H:K@<DCH
B69: >C8:A@JAJ G:L=:G I=: K@G67>AND; I=: GH@GH: 9: 8G6H:9 6I
=>=:G 8:A@JAJ G: 8DC8: CI@I>DCH D; 8J@JB>C ; K:G6A;68IDGH6N
=6K: 8DCG>7I:9 ID I=: K@G67>AND; I=: GEH@H ID 8J@JB>C 6I
AD: G9DH:HD; 8J@JB>C >@A9>@< I=: ;G FJ:C8ND; 9D>@< I=: A:C<=
D;IG6IB: CI 6C9 I=: >@KAKB: CI D;I>HJ JEI6@:IGCHE@GIG;DG8JG
8JB>C 'D C:I=: AHH@DG9>H6 H: BD9:AHD; 86C8: G I=:G 6EE:6GHID 7: 6
G A@<DCH=>E7: IL :: C I=: 9DH: D; 8J@JB>C 6C9 >HIG6IB: CI ; ; 8IH
L=>@< HJEDGH6 HE8>>8 >@< @<DC7: IL :: C' ú 6C9 8J@JB>C >C
I6G: I>@< 86C8: G C DI=: GD7H:K@<DCB69; ;@B I=>H@<ANHL6 HI=6I
I=: =>=:HI 6K :HI>B6I: 9 ;DG8J@JB>C ID :A>8>I6 HB >A@<IG6IB: CI ; ;
; 8I D; 8J@JB>C;D@AD >@< D@A6C9 ") 9D>@< >@<C8C8: GEG8A G86ABD9
:AHL6H C< B% Z& 6C9 C< B% Z& GHEB I>K:AN
=: :H :HI>B6I: 9 8DC8: CI@I>DCH D; 8J@JB>C 6G AD: G I=6C I=:
Đ Z& G@< D; 8DC8: CI@I>DCH D; 8J@JB>C I=6I L: G: D7H:GK9 ID
>G>@< I=: 68>K@<DCCD; ' ú 6C9 GA6H D; 8ND@<H>C8: A@JAJ G:
HG@<ANH<@< H>@< 6HEGK@DJH9>@<HJH9 I=6I I=:G 6G 6CJB 7: GD;
>68IDGH=6I B6N8DCG>7I: ID I=: AD B: 6HJG 9 E@H6 8DC8: CI@I>DC
D; 8J@JB>C 6HH@<6I:9 L>I= >HIG6IB: CI ; ; 8IHin vivo
"C8DCGH ID L= 6I L6 HD7H:GK9 >@<C6B ABD9:AHD; 86C8: G;DG>C
>A6B B6 I>DCN>H6 H: BD9:AH I=:G L6 HCDGA@<DCH=>E7: IL :: C 9DH:
6C9 I=: IG6IB: CI GH@GH:ID 8J@JB>C I=: G@< D; :HI>B6I: 9 6K K6A
J: H;DG8J@JB>C >CEG8A G86ABD9:AHD; >C6B B6 I>DC;D@AD >@< D@A
69B>C>H@I>DC6C9 >O6EG>DC:6A69B>C>H@I>DCG@<@< ;@B ID
C< B%)DH>A G6H@<DGI=>H>C9>@< 6G 9>@<HJH9 7: AD

Fig. 3. +: A@<DCH=>E: IL :: C I=: D H: D; J @JB>C 9 B>C>H G9 (G6AN6C9
I=: -G:6IB: CI ; ; 8IHD; J @JB>C>C)G: 8A G86A C -B6 A&D9:AHD; 6 C8: G = :
D@A9DH: D; 8J@JB>C 69B>C>H G9 :>I=:G >CI=: 9@I) 6CA DG6H6 ;>M9
9DH:) 6CA H@<DL>C-6 7A L: G: E@I: 9 6<<@<H I=: IG6IB: CI ; ; 8IHD;
8J@JB>C

Fig. 4. +: A@<DCH=>E: IL :: C I=: D H: D; J @JB>C 9 B>C>H G9 "O6EG>
IDC:6AN6C9 I=: -G:6IB: CI ; ; 8IHD; J @JB>C>C)G: 8A G86A C -B6 A&D9:AH
D; 6 C8: G = : 9DH:HD; 8J@JB>C 69B>C>H G9 >O6EG>DC:6AN6C9 H@<DL>C>
-6 7A L: G: E@I: 9 6<<@<H I=: IG6IB: CI ; ; 8IHD; 8J@JB>C

7. Data interpretation, summary and conclusions

=: : EJC@<D; I=>H@<K>L L6 HID>@<H><6I: 9>; I=:G L6 H6 E@<HJH>
7A G A@<DCH=>E7: IL :: C I=: 68>K@<N D; 8J@JB>C >C8: A@JAJ G: 8JG
8JB>@<H@<6IB: CI ; ; 8IH>@<C6B ABD9:AHD; 9>H6 H: 6C9 I=: E=6@<6
8D@<G: I>@<D; 8J@JB>C >G8I I6G: I>@<D; ' ú 6C9 ' ú B: 9@<I: G:
H@<GH: H7N8J@JB>C L6 H8=DH: C:ID 8DB E6G: 8J@JB>@<H@<A@JAJ G: 68

I>K>NL>I= >H68>K>N>CEG8A>G86AGD: CI BD9:AHD;86C8:G6C9 >C>6B
 B6IDGN9>H6H: 6HI=: >C: 68>DC7: IL :: C ' ü 6C9 8JCB>C =6H
 7:::C L: AA>C:H>6I: 9 6 H:9 9616 :M>H>G >CI=: A<C6IJG:6C9 BDG:
 G8:CI 9:K:ADB: CIH>CI=: JC9:GH6C9>G D; =DL 8:AM=6C9A 8JG
 8JB>C EASJH7A :MEACB>DGHID I=: G6HDL=N=>=:G8DC8:CI6
 I>DGH;8JCB>C 6G GFJ>C ID >C: 68 L>I= ' ü >C8:A&AJAJG:
 8DB E6G9 ID I=: :HI>B6I: 9 E&HB6 8DC8:CI6I>DGH; 8JCB>C I=6I
 :A>8I9 ;;: 8I>K: IG6IB: CI >CGD: CI BD9:AHD; 9>H6H: L: G: E&K9: 9
 6C9 6G HJB B6G9>9 >C >> J G=:GBDG: E=6C68D@>:I>8 G6HDL
 L: G:E&K9: 9 ID=: AEME&:CI=: 68>K>ND;8JCB>C>CGD: CI BD9:AH
 D; 9>H6H: L=: C 69B>C>H G9 :>I=:G D&GANDG>CGE>GDC:6AN
 GDB 6C6C&HHD; I=: 8:A&AJAJG: 9616 ;DG8JCB>C H>K>G6A@N
 ;; 6IJGHD;8JCB>C L: G:CD: 9 >GHN I=: ;;: 8IHD;8JCB>C L: G:
 8DC8:CI6I>DC9: E:C9CI L>I= 6 HB >A&G6C< D; 8DC8:CI6I>DGHED
 9J8>G 6 9>G8I >G>7>DC ' ü 6C9 ' ü B: 9>6I:9 8ND@G:
 8=>B D@C GA6H AD: G 8DC8:CI6I>DGH; 8JCB>C 9>H&N>G 6
 <G6I: GK6G7>AND; >G>7>DC 6 8IDGH=6I B6N=6K: A@ANE&N9 6
 GDA: >C8JCB>C>H&: A&AJAJG: 68>K>NL: G: I>B: D: MEDHJG: ID 8JG
 8JB>C 6C9 :K9: C8 ;DGAID<AK: 9 6C9 EDH7A >GK:G7A: >G>7>DC
 D; >H8:AA&6I6G: IH >K:C I=: :K9: C8 I=6I 8JCB>C JHH 8:AA&6
 JEI6@:IGCHEDGIGH I=:>GEGH:C8: DGA&@I=:GD; DCI=: 8:A&B: B
 7G6C LDJA9 8DCI>ZJ: ID I=: K6G67>AND; 8JCB>C>H&8>K>N :HE:
 8>6AN6I AD: G8DC8:CI6I>DGH;8JCB>C L=: :G I=:G LDJA9 7: AHHD;
 6 9GK<C<;DG8 ;DGHBA EA 9>;JH&CD; 8JCB>C 68GDIH=: 8:A&B: B
 7G6C DGHBA EA 9>;JH&CD; 8JCB>C 68GDIH=: 8:A&B: B 7G6C >C
 8G6H>G I=: >GJ76I>DCI>B: 6C9 8DC8:CI6I>DCL>I= 8:AMLDJA9 ;6KDJG
 <G6I: G6B DJCIHD; 8JCB>C:CI: G>G I=: 8:A&C9 =: C8 6 <G6I: G7JI
 AHHK6G67A: 68>K>NL=>8 L6 HD7H:GK9 'D C I=: AHHI=: G6=:G>=>=
 8DC8:CI6I>DGH; 8JCB>C GFJ>C ID :A>8I8: A&AJAJG: GHDGH:6G
 A@ANGA& 9 ID >HEIDGH7>N =>=>= E&I: >C7>C9>G 6C9 6 BDHAN
 9>;JH&C9DB >C6: 9 GDI: D; 8: AACIGN

K 9: C8 L6 HEGH:CI:9 >C>8>G I=6I 8JCB>C 86C 9>G8IAN>C
 =>7>' ü >CGD: CI BD9:AHD; 9>H6H: 6C9 9: HEI >HEIDCE=6C68D
 @>:I>8 E&A: 9>HG>ZJ: ID I>HJH>C6C: MEDHJG: I>B: 9: E: C9CI B6C
 C:G = JH 7NK>G: D; >H>G>7>DCD; ' ü 8JCB>C LDJA9 7: :M
 E:8I:9 ID 7: 68>K: >C9>H6H: BD9:AHJ&B=6H86C8:G6C9 >C>6B B6I>DC
 =>HL6H>G: :9 I=: 86H: 6C9 8DB E6G9 ID I=: =>=>= 8DC8:CI6I>DGH;
 8JCB>C GFJ>C ;DG68>K>N 6I ' ü >C8: A&AJAJG: 8JCB>C L6H
 8A6 G&68>K: 6I 8DCH9:G67ANAD: GHI>B6I: 9 E&HB6 8DC8:CI6I>DGH>C
 GD: CI BD9:AHD; 9>H6H: L=: I=: G69B>C>H G9 D&GANDG' (C: EDH>
 7A :MEACB>DC;DGI=>H9>; GC8: >H=: >KDAKB: CI D; JEI6@:IGCH
 EDGIGH>CI=: 8:AA&EI6@>D; 8JCB>C >C6C>B6 AH"C 6C>B6 AHJEI6@:
 IGCHEDGIGHLDJA9 A@AN7: DB>B6 AN:MEGH9 >C8DB E6GHD ID 8: AA
 AG: H6C9 EGB6 G8: A&AJAJGH>CL=>8 IGCHEDGIGHB6N7: EDDANM
 EGH9 DG67H:CI ;DB I=: E&HB6 B: B 7G6C D; I=: 8:AAID L:K:G
 L=>AI=: >KDAKB: CI D; JEI6@:IGCHEDGIGH>CI>HJH B6NE&K9: 6C
 :MEACB>DC;DGAID: G;;: 8I>K: :HI>B6I: 9 6K6C< E&HB6 8DC8:CI6
 I>DGH8DB E6G9 ID 8: A&AJAJG: DI=: G:MEACB>DGH;DGI=: 9>; GC8: 7:
 IL :: CI=: 8: A&AJAJG: 68>K>ND; 8JCB>C 6C9 >H68>K>N>CEG8A>G86A
 6C>B6 AH&@ANM>H&HJ&B=6HI=: ED: CI>6AD; 8JCB>C ID >GK: G7A>N>C
 I: 68 L>I= >HI6G: IH6C9 I=: >BE68I D; AD<GE&HB6 :MEDHJG: ID 8JG
 8JB>C DCI=: I>B: 9: E: C9CI >G6H9 688JB A&DCCD; 8JCB>C >C
 I>HJH C DI=: GE&JH7A :MEACB>DCB6NA> >CI=: A&C CJB 7: GD;
 B: I67DA> HE&9J8: 9 7NI=: B: I67DA>H B D; 8JCB>C "B EDG6CI GAH
 ;DGI=: E=6H "" B: I67DA> D; 8JCB>C 8JCB>C <A8JGID9: 7DI= 6H
 6 HDG: ;DGE&HB6 6C9 I>HJ 8JCB>C I=GD<= B: I67DA>H 7N p
 <A8JGID9>H 6C9 6H6 IG6IB: CI ;DG: JG6C>6B B6I>DC=6K: 7: :C
 E&EDH9 4 5 "I=6H7: :C 9: BDCHG6: 9 >C>8: I=6I D&A69B>C>H
 I6I>DCD; 8JCB>C GHJAH>C6 =>=>=G66D; 8JCB>C <A8JGID9: ID
 8JCB>C 8DB E6G9 ID ") 69B>C>H6I>DC7N ;DA9KH ;DA9 GHE8
 I>K: ANI 5 EG&E6A&9J: ID I=: =>=>= 9: <G D; <A8JGID9: 96I>DCC&JG
 G6<6I I=: >C: HIC6A7G7H 7D9: GB: B 7G6C >CGD: CIH "C 699>DC

CORRECTED

Fig. 5. ,8=: B6I>8 9>6<6B H>DL>G =DL I=: :CI&ND;8JCB>C>D8:AM>C8:A&AJAJG:6C9 >C>HJ 9>; GH>C8:A&AJAJG: , EGH:CI>CI=: 8JAJG:B: 9>JB 7>C9H
 8JCB>C 6C9 =: AEIDH7A>9>I CDD:I=: AHHHIB: 6<<G<6I>DCD;8JCB>C B6ND8JG G: 8JCB>C 688JB A& H>Q=: 8:A&B: B 7G6C 6C9 9>;JH>H>D I=: 8:AM
 ID>C: 68 L>I= ' ü 6C9 L>I=>Q=: 8:A&CJAJ H =: :MEGHHD;JEI6@:IGCHEDGIGH>: (-) 6C9 (- >HA@ANAB >I9 DCCD :M>H CI 6C9 9>;JH&C>HA@AN
 I=: 9DB >C6CI E6=L6N;DG8JCB>C ID <6C88: HI>D8: AM>C8:AJAJG: "CEG8A>G86A6C>B6 AHU9>:H8JCB>C 9DH9 D&GAN>H&DCK: G19 ID 8JCB>C <A8JGID9: 6I
 I=: >C: HIC6A7G7H 7D9: GB: B 7G6C 6C9 L>I=>CI=: AK: G L=>A L=: C 9DH9 >DGE&GDC: 6ANBDCK: GHDCID 8JCB>C <A8JGID9: D&JG>H>CI=: AK: G 0= >A 8JG
 8JB>C >H>=>=AN7DJC9 ID E&HB6 E&I: >GH 8JCB>C <A8JGID9: >HAHH7DJC9 6C9 7: II: G9>HG>ZJ: 9 ID I>HJH J CB>C p <A8JGID9>H 7G6 @HDL 8JCB>C
 <A8JGID9: ID ;G: 8JCB>C 6C9 ID<I=:GL>I=:G: 8JCB>C CD 7DJC9 ID E&HB6 E&I: >GH86C7: I6@C>D8: AM7NI=: EG9DB >C6CI E6=L6N IGCHEDGIGB: 9>
 6I:9 JEI6@:K6L: AAMEGH9 JEI6@:IGCHEDGIGH (-) 6C9 (- 6C9 ID 6 AH&GMI: CI 9>;JH&C J CB>C <A8JGID9: B6N6AH7: I6@CJE >D8: AM6C9 8DC
 K:G19 ID 8JCB>C 7N8: AA&68JCB>C p <A8JGID9>H ->HJ 8: AM6G I=:G ;DG: MEDH9 ID ;;: 8I>K: IG6IB: CI AK>AH; 8JCB>C 8DB E6G9 ID I=: G/6I>K: ANAD
 AK>AH; 8JCB>C B: 6HJ9 >CI=: E&HB6

I=: E#H6 I: B>C6A=6A;A> D; 8JGB>C <A8JGD9: L6 H;DJC9 ID 7: ;DA9AD<G I=6C 8JGB>C ;DAAD >G: DGA69B>C>H6I>DCD; C6CD :B JAHDC8JGB>C ID B>8: 4 5 >K:C I=6I 8JGB>C <A8JGD9: >H BDG: HAJ7A I=6C 8JGB>C 6C9 A@AN>HA>HE#H6 EGI: >C7DJC9 >I LDJA9 BDG: G69>N <6-C688: HHD I=: >G: GH>6AH#8: 6C9 I>HJH 6C9 HJFH:FJ:CIAN 7: 8DCK:G19 ID 8JGB>C 7N I>HJ p <A8JGD9>GH p <A8JGD9>GH 68>K>N K6GN<G 6B DG>H I>HJH J GB>C LDJA9 I=:C 7: 6K>67A:;DG9>;JH6C6C9 68>K: JEI6@>:DD IJBDJG8: A#>C8DCH9 :G67AN<G I: G6B DJCIHI=6C E#H6 7DJC9 8JGB>C 6HL6 HD7H:GK9 ;DGIJBDJGAK:AH; 9DMDG7>8<C ;DAAD >G I=: 69B>C>H6I>DCD; 9DM DG7>8<C p <A8JGD9>G 4 5 "C 699>DC (-) JEI6@:IGCHEDGIGH =6K: 7: :C ;DJC9 ID 7: DKGMEGH>H9 >C6 CJB 7: GD; HDA9 =JB6C IJ BDJGH4 5 6C9 p <A8JGD9>GH 68>K>N>CIJBDJGI>HJ >HA: K6: 9 4 5 -- :G ;DG: I=: IG6IB: CI;; ; 8I D; 8JGB>C>CEG8A>G86A6CB6A BD9:AH6I AD: GHI>B6I: 9 E#H6 8DC8: CI@>DCH;DAAD >G: DGA6C9 >C IGEGHDC:6A69B>C>H6I>DC8DB E6G9 ID >H8: A#AJJG: 68>K>N B6N 7: GA6: 9 ID I=: EG#C8: D; =>:G6B DJCHD; 8JGB>C p <A8JGD9>G >C IJBDJGH L= ># LDJA9 7: 8DCK:G19 ID 8JGB>C 7N p <A8JGD9>GH 6C9 GE9AI I6 @>C JE 7N (-) JEI6@:IGCHEDGIGH =: K6G7>AN>C I=: :MEGH#D; I>HJ (-) IGCHEDGIGH B6N8DCI>G: I: ID I=: H6I: G >CI=: 96I6 GA6>G I=: 9DH: D; 8JGB>C ID >HIG6IB: CI;; ; 8IH J G 8JB>C <A8JGD9: B6N 6A#D=6K: E#N9 6 8G>H6AGA: ;DGI=: 7: II: G 9>HG7J I>DCD; 8JGB>C >DD 9D< I>HJH L>I= AD<G >C IJHDC I>B: H =: 8DCK:GHDC D; 8JGB>C <A8JGD9: ID 8JGB>C 7N p <A8JGD9>GH >C I>HJH B6N 6A#D8DCI>G: I: ID I=: IG6IB: CI;; ; 8IH>C G19: CI BD9: AHD; >C6B B6 IDGN9>#6 H:HD7H:GK9 6I AD :HI>B6I: 9 6K 8DC8: CI@>DCH; 8JGB>C p A8JGD9>GH 68>K>N>H6I>DC8 H9 6I I=: H# D; >C6B B6 I>DC6H6 8DCH:FJ:C8: D; C: JIGDE>A>CAGI>DC4 5 "C 8DC8: GIL>I= 8JGB>C <A8JGD9: 6C9 JEI6@:IGCHEDGIGH EGH:CI DC>C6B B6 IDGN8: AA I=: B: I67DA#B D; 8JGB>C <A8JGD9 7N p <A8JGD9>GH ID 8JGB>C 6C9 I=: GHJA>G 68>K: JEI6@>:DD 8: AA B6N=6K: GHJA9 >CB: 9>6I>DCD;>HIG6IB: CI;; ; 8IH6<6>CH>D68: A AA6DM4#K: B: I67DA#B H6I AD: GI=6C:ME:8I:9 E#H6 8DC8: CI@>DCH; 8JGB>C4 5 =>:G: D; K6G7>AN>CI=: 9: <G D; I=: >C6B B6 IDGNH6DCH: ID 8JGB>C>C6C>B6 ABD9: AHD; >C6B B6 I>DCB6N=6K: 8DCI>G: I: ID I=: >G7>AN ID D7H:GK6: 6 GA6>DCH>E 7: II: : C 8JGB>C 9DH: 6C9 IG6IB: CI;; ; 8IH >K:C I=: :K>9: C8 >I LDJA9 6EE:6GI=6I I=: 8DCK:GHDC D; 8JGB>C <A8JGD9: ID 8JGB>C L>I>=C I>HJH B6N=: AED:ME#>C I=: GA6>DCH>E7: IL : C I=: AD: GI=6C:ME:8I:9 E#H6 8DC8: CI@>DCH; 8JGB>C I=6I B: 9>6I: >HIG6IB: CI;; ; 8IH;DAAD >G: DGA6C9") 9DH>G 8DB E6G9 ID >H68>K>N>C8: A#AJJG: "; HJ>=H=: 86H: <K:C I=: ;>C9>G I=6I CD BJ 8=9>; GC8: L6 HD7H:GK9 7: IL : C I=: :HI>B6I: 9 6K 6C9 IG6IB: CI;; ; 8IH;DG8JGB>C;DAAD >G: DGA6C9") 69B>C>H IG6I>DC >I>HA@AN=6I 7DI I=: AK:G6C9 >G: H>C: E6K9: BDG: I=6C 69: FJ6I: AK:AH; I>HJ 8JGB>C <A8JGD9: ID B: 9>6I: >HIG6IB: CI;; ; 8IH >I= GHE8I ID I=: IG6IB: CI D; 86C8: GJH>G 8JGB>C >HL: AA @DLC 6C>6C>D>: C# ; ; 8IH=6K: I=: JC9: H67A: ; ; 8I D; G9J8>G I=: :MEDH:G: D; I=: IJ BDJGID 8JGB>C D>9I 6C6EE6GCI 8G>H6A;68IDG AB >#>G 8JGB>C>HIG6IB: CI;; ; 8IH 'D C I=: AHH;D6J A6>G 8JG 8JB>CHD=6I >HEDDGE=66B 8D@G: I>8 EDEEG>H EDDE7>D6K6>#7>AN H>DG E#H6 =6A;A> 6G >BE6K9 6H>H=: 86H: ;DGC6D;DGBJ/6I:9 8JGB>C4 5 =6HGHAJ9 >C7: II: GIG6IB: CI;; ; 8IH 0=: :I=: GI=: 7: II: GIG6IB: CI;; ; 8IH6G >I=:G9J: ID 6A#D<G: MEDH:G: ID 8JGB>C DG 8DCH:FJ:C8: D; 6G#A: ;DG I=: BDG: HAJ7A B: I67DA#B HD; 8JGB>C 8JGB>C <A8JGD9: 8JGB>C HAJ9: H>DJA97: :6A/6I:9 6 H9 DCI=: 6C6AHHD; I=: GA6>DCH>E7: IL : C 8JGB>C>H6I>DC8: A#AJJG: 68 I>K>N E=66B 8D@G: I>#H6C9 68>K>N>C6C>B6 ABD9: AHD; 9>#6H: EG H:C I:9 >CI=>HGK>L 8: A#6H9 :ME: GB: CIH6G 8A6 GNK: GN>BEDG6CI ;DG>9CI>;N>G ED: CI>6A8JGB>C I6G: IH;DGI6 I>G 9>#6H: >CEG 8A>G86A6CB6 ABD9: AH9: HE# I=: =>: 8DC8: CI@>DCH; 8JGB>C: B EADN9 ; K:G6AG6H#HL: G: E6K9: 9 ID: ME#>C I=: AD: GED: C#ND; 8JGB>C>C8: A#AJJG: 8DB E6G9 ID: HI>B6I: 9 6K>C6C>B6 ABD9: AHD; 9>#6H: 6I DC I6G: I ;DG8JGB>C ' ü -- JH :ME: 9>#>DJH#G: C 8: AA

8JAJG:ME:GB: CIHL>AAGB6>C6C>BEDG6CI BD9: A;DG>9CI>;86I>DC D; I=:G6E: JI>8 I6G: IH;DG8JGB>C>CI=: ; JIJG: "B EDG6CI 8DCH9: G6 I>DCH;DG:AJ8>96I>G I=:G6E: JI>8 I6G: IH ;DG8JGB>C >C8: A#AJJG: H>DJA9I6@>:DD 688DJCI I=: ED: CI>6A68>K>ND; 8JGB>C <A8JGD9: 6C9 >C<: C:G6ABDG: HAJ7A A#HEGI: >C7DJC9 B: I67DA#B HD; 8JG 8JB>C in vivo 6C9 I=: 68>K>ND; 8: AA#AJJG I6@:IGCHEDGIGH "C 699> I>DC BDG: ;D8JH#DJA97: EJI DC:AJ8>96I>G I=: G#A: D; I=: HAJ7A B: I67DA#B HD; 8JGB>C>CI=: B: 9>6I>DCD; 8JGB>C>HIG6IB: CI;; ; 8IH in vivo 0= >A8JGB>C 6C9 >H>B: I67DA#B H6AD C6NCD E6G9J8: 6 HG I=:G6E: JI>8 ; ; 8I I=:N B6N>GJ8: 6 8: AA#AJJG I6@:IGCHEDGIGH: CII=6I :C=6C8H I=: 68>K>ND; I6G: I: 9 9G>H>CI=: IG6IB: CI D; 9>#6H: "C I=>HG<6G9 8JGB>C 8DB 7>C: 9 L>I= 8NDIDM8 6C>86C8G9G<H=6H6A G69NH>DL C>BE6K9 I=:G6E: JI>8 DJI8DB: H7DI= 6H6 GHJAID; G9J8 >G I=: IDM8>ND; H6C9G6G9CI>86C8G I=:G6E: H6C9 9J: ID >H>D>G>G#8 6C>86C8G 68>K>N 4 5 0>I= GHE8I ID I=:) "" , 68>K>N D; 8JG 8JB>C 8DB EDJ9HEDH:HHG) "" , 6C9 I=: ED: CI>6AID 6<<G<6I: 6G BDG: A@AN EDH:HH6D I6G: I668>K>NL= ># >H6H#6I: 9 L>I= 6C >G6H9 EDECH#N ID 7: IDM8 6I E=66B 8DAB>86A#GAK6CI 9DH7A 4 5 =>H9D: H CD 6EE: 6GID 7: I=: 86H: ;DGD6AN69B>C>H G9 8JG 8JB>C 8JGB>C>HG#K: ANDC IDM8 :K:C >CI=: >G: H>C: L=:G I>H HJ :MEDH:G#H 6G =>: 4 5 &6 CNH:88: H#JA 6II: BEIH=6K: 7: :C B69: ID >G6H: I=: 8DC8: CI@>DCH; 8JGB>C>CI=: E#H6 ;DAAD >G: DGA6D#G: GHJA>G >C>G6I: GIG6IB: CI;; ; 8IH =DL :K:G I=:G >H6A L6N#6 GH@=6I JCL6 CI:9 8JGB>C IDM8>H 6C9 9G< 9G< >G: 68 I>DCH B6N 6G#H 4 5 =: JH D; 8JGB>C <A8JGD9: 6H6 6H6D9>C<O 4 5 ID H#E#A I>HJH L>I= 68>K: 8JGB>C >H6 G6H#67A: 6A: G6#K: 6EE6G I= ID 7: 8DCH9: G9 >CI=: 9: H#C D; 8JGB>C 6C6AD>HL>I= 6C :K:C AD: GIDM8 A67>#N =: DB>B>O6>DCD; 7: II: G9>HG>J I: 9 8JG 8JB>C 6C6AD>HI=6I 86C 7: G69>N 68: 9 JEDC7N8: AA#AJJG I6@:IGCH EDGIGH#DJA9#ADY: 8DCH9: G9 6H6 L6 NID 7DD#H8: AA#KAH6C9 IG6 I B: CI;; ; 8IH6AD DG>C8DB 7>C6>DCL>I= @DLC I=:G6E: JI>8 9G<H

Uncited references

CRediT authorship contribution statement

Gordon T. Bolger : D C8: EIJ 6A>@>DC 6 I6 8JG6DC 0G>#>G & D DG<C6A9G; I 0G>#>G & DGK>L :9>#>G Kresimir Pucaj : D C8: EIJ 6A>@>DC Yvonne O. Minta : D C8: EIJ 6A>@>DC 0G>#>G & DGK>L :9>#>G Peter Sordillo Minta : D C8: EIJ 6A>@>DC 0G>#>G & DGK>L :9>#>G

Declaration of Competing Interest

=: 6J I=D6I9: 8#G I=6I I=:N =6K: CD@DLC 8DB E: I>G: ;C6C8>6A >G: GH#H DGE: GH#6A GA6>DCH>E#I=6I 8DJ9 =6K: 6EE: 6C9 ID >CAJ :C8: I=: LDG@EDG9 >CI=>HE6E: G

Data availability

'D 96I6 L6 HJH9 ;DGI=: GH:6G=9: H6#>: 9 >CI=: 6G>8A

References

4 5 , \$ 6C9JG & \$)6C9N , J C< \$, = C & J G@B> ; I=>) %B I G@A/ 6 9B 6: K < <6GL6A J G8B >C9: B: I=DNW8JGB>C 7#H9 :I=DNW8JGB>C I: IG=N9G8JGB>C 6C9 IJB: GD: H9>; :GCI>6AN G>J#A: 6C>>C6B B6 IDGN6C9 6C>E#A: ;G I>K GH#DCH I=GD<= 6 + (, >G: E: C9CI B: 8=6C>B 6 G8D<C: H#H D =I#H 9D>DG 86G8C7>B

4 5 & !: G#G + K6C DAC & GD: @66G9C & &#>A =: BDA8JA676HH ;DGI=: E=66B 8D@G: I>8H6C9 E=66B 8DNC#>8D; 8JG8B >C6C9 >H>B: I67DA#B >CGA6D8DCI 86C8G) =66B 8DA >: K D =I#H 9D>DG EG

4 5 \$ & ' : ABC # % 6 =A># >HBC # G6=6B)6JA> & 06 AIGH =: :HH>C#>#>B >HND; 8JG8B >C# & : 9 =: B D =I#H 9D>DG 68H?B: 9 8=>B 7

4 5 \$ " G>N96G16>=: 8=:B >HND;8JG8B >C;DB :MIG8>DCID I=:G6E J 8
6<C I & DA8JAH D =IEH 9D>DG
BDA8JAH

4 5 & : G6' =:6B6 & = DH %!J NG= , # %: - &>C - \$L DC \$
:DG '6 CDGBJ/6I>DHD;8JG8B >C6C:B :G<C<E6G9>B ;DG>BE@K9
GB: 9:6A6EEA>I>D (C 8D6Gd D 9D>

4 5 ' DAO& 9 6H: & ,8=Q:9:G-DL6 G96CJ9C: G8C9>G D;E6C 6HHN
>Q:G;C8: 8DBEDJ9H6C9 E@B>HJ>N 6 HG:8JG6AE: GE: 8I>K DC7>C9>G
BD9: H # =:B "C; D9: A D 9D>

4 5 ! 2J % %S 3 3=6C< ! 3=6C< ! !J -6 Gd >G' ü E@L6N;DGI=:
I=:G6END;9H16HH B: 8=6C-B 6C9 8A6G8AHU9N ,>C6A6C6H98I -6 Gd =:G
=IEH 9D>DG H

4 5 ! 3=6C< , 'J C' ü >C>6B B6I>DC6C9 G9C6A9>H6HH : AA>DIB>
=IEH 9D>DG H

4 5 + ! ,>= 2 06 C & 26C<' @E@ H>C6A>G E@L6NH>C
C:J@D>>A>C6B B6I>DC 6 B>C>GK>L GDQ & DA' : J@DIB> 9D>

4 5 ! %> 3=DC< * 06 C < 0 =:C 2 2J6C J G8B >C>H6C) G9DM
>G>7>D6C9 :M=>7>H6C6C>K>G68>K>N 6<6>C>H \$, ! / GE@>I>D 6C9
E@L6N;DGI=: H B: 8=6C-B 6C9 8A6G8AHU9N ,>C6A6C6H98I -6 Gd =:G
=IEH 9D>DG H

4 5 ' %66C6 >6B6 +DB: GD>>J:A & : H@ & % ,DID & DCI<C< GD C
JE96I: DCI=: :MEAD6IDUJH D;8JG8B >C>CC:J@DIB>=>G>C89>HID9GH
C I>DM9CQH =IEH 9D>DG 6C>DM

4 5 + G>:A, G>:A>: HMG% 0: >H ,8=WC A:7 - &6<C H +69A - DA>G
(/ :A6G) ,DG9AD E=6H 9DH :H86A6DCHU9NDCl=: H6: IN DA:G7>A>N
6C9 68I>K>N D; AEDH6A8JG8B >C %>E@B>G- & >CE@>C IHL>=: A@B6A
69K6C89 DCB: I6H6I>886C8G 6 C8 G =:B D=: G)= 6C68DA
D =IEH 9D>DG H

4 5 ! (O6L6 "B6O>B 2 ,J B> - !6 H>BDID & \$6C6 2 &6 @GD - !HJ96
' -6 @66H> ! \$6@N6 J G8B >C >A8J@C9 E@NH6C>BED6G6 G@: ID
>:E =>: A>K>AHD;G: ;DGB8JG8B >C>C=: 7AD@ >DA)= 6C6 J AA
D =IEH 9D>DG 7E77

4 5 (A>K66 - 0 & DDG7 !J 6) GDLC ,J C7 %@I67 #)
,CN9G7 2 2DD@ ! ,=>B9 " &6G8H ! &>A6G - 0 0)6:8 "C>7>D>C
D I=: ' H>C6A>G E@L6N7N I=: 8JG8B >C6C6A< 7H
ENG9>CABI=:NA9: C: E=:G9DC: 6C>>C6B B6IDG6C9 6C>86C8G
E@EG>H "C "B B J CDE=6C68DA D =IEH 9D>DG
?>C>BE

4 5 , , !6 C 2 , \$: JB ! # : D 2 # ,J G = J G8B >CH.EEGH1H 68I>K6>DCD;
' ü 6C9) >QJ8:9 7NE=DGD>H I: G>C8JAU9 =JB6 C E@B N: A@B N-8
AJ@B >68: A@ # >D8: B & DA >DA D =IEH 9D>DG
7B7GE

4 5 \$, C % 68 @G C I>DM9C 6C9 G9DMG<JA6DCC;<: C: I@GCH6E I>D
' # D 9D> ;6H??

4 5) 6 G@H & \$6G6 'J 8A6 G;68IDC 6 E>K6AIG6CH6E I>D;68IDC>G=GID:8
>C6B B6IDG6H6HH ' C < # & 9 D =IEH 9D>DG
&

4 5 & >6C86A66 '6 I6C & # %C6G@ + : GHI ' ü GAHJJC>:M8=6C<:
DC6 E=NHDA>86A I: H8A |GD I>C,8> D =IEH 9D>DG
E@

4 5 J =@66CC & D76H>G> J H@ A9>C<G + ,!6=A66C & DCI6HG>
' =@6>: > J G8B >CDB9JAH HC:J8A6G;68IDC ' ü B: 9:6I:9
>C6B B6I>DC>C>JB6 C I: C@B N: H>C>K>G G@: D I=: E=DIE=6I>9NA@HDA
>G@: @ I E@L6N # >DA =:B D =IEH 9D>DG
?7&

4 5 1 6 D # \$JD ! #6C< : :7 2 %J >K<: + = 6E6B C ,
J A@6KH@N 6 JI6B6 "B B J CDB9JAH6G68I>K>N D;8JG8B >CH.EEGH1H
D; A@B E=D8N: E@A;G6I>D 9: K:A@B:C I D: 8: A@B: 9:6I:9 8NDIDM8>N 6C9
8ND@G: E@9J8I>DC>C>K>D >D8: B) = 6C68DA D =IEH
9D>DG 778E

4 5 2 \$6C< 2 # ,DC< \$ & \$>B 2 \$ = D: , 2 !L 6C< - , \$>B J G8B >C
>G>7>H= 8ND@G: E@>A>C = 8: A@7NH.EEGH1H>G>C: G@ @G
E@9J8I>DC>C68D@E=6<: H G #) = 6C68DA D 9D>
H7?E

4 5 , \$DC9GJ %: # %>J G8B >CH.EEGH1H ' !> >QJ8: 9 1 %
:MEGH@CK6 >G>7>D>C D; E@H1K: "\$ \$p E@L6N6C9 JE G<JA6DCC; C: <6I>K:
&S) E@L6N,8>+ E 9D> H@E

4 5 +6=6G9D 0>9768QD ! ,J J> \$ \$: B6C J G8B >C9: 8G6H9 A>K: AD;
E@C: A@B 6ID@8ND@G: H>C@BDC@B: 8JAU>G: MEH9 ID EG 8A@E I>8E@H6
7N6;> 8I>G> I=: I@GCH6E I>D;68IDG' ü 6C9) + > >DB6@>: CDB>8 & 9
D =IEH 9D>DG ?EG<N

4 5 #D7>C G9=6B &) +JH@ #J B6 , '6 GJA 6 C:CC:G +
6 ADJG,6 GDG J G8B >C7AD@8ND@G: B: 9:6I:9 ' ü 68I>K6>DC6C9
E@C: A@B 6ID@<: C: MEGH@C7N>G>7>D>C<>G>7>DGN68IDG ' ü @G@:
68I>K>N # "B B J CDA D =IE LL L ?B B J CDA>C<
8DCI C I

4 5) ! \$>A@C \$@C@H@ \$ & >8=6A @ (6 G7>G> , HI>6C D)
,DBB :G=D; .) ; ; : G : GA@ 6 8=6: >G J G8B >C>G>7>H@E@H6I:
86C8GB: I6H6I>H>K>K>D7N I6G>I>G> I=: >C6B B6IDG6ND@G: H 1 % 6C9
6 G8>C>: H>H D =IEH 9D>DG 86G8C7>H

4 5 K@C@>G9 ' & A>A>K: CH # & G I>?C, ->B6A #) D CCAAN- # & 9:
0>I I: % & @67: I +DA: D;8JG8B >C6C9 I=: >G>7>D>C D; ' ü >C I=: DGH D;
8=:B D I=: G@EN>QJ8: 9 B J D H@76G6G>C7JGN%J @B >6 D 9D>

H7AJ

4 5 C ID>C # ,>B6G9 >G69 J G8B >C>G>7>H6<C I >QJ8: 9 =JB6C
C:J I G@>AJC8>D>H>C>K>D 6C9 A@E@DAN@H8=6G9: >QJ8: 9 C:J I G@>A8
>C>A@B>DC>C>K>D "C "B B J CDE=6C68DA D =IEH
9D>DG ?>C>BE

4 5 % %> , G6=: + \$ J G@B @>E@H@B: :C8E6H6I:9 8JG8B >C>C>K>D 6C9
>C>K>D: ; 8IHDCE@A;G6I>D 6EDH6H H>C6A>G 6C9 6C<D>C<: H>H 6 C8G
D 9D> 8C8G

4 5 * %J 0 - 2 %D , 0 ,O: 2 -DC< J G8B >C>G>7>H8: A@E@A;G6I>D D;
& & 6C9 - 7G6 H I86C8G8: A@B: 9:6I:9 7N9DLC G<JA6DCC;'
' ü 8N@C 6C9 & &) I@GCH6E I>D) = NDB: B D =IEH
9D>DG ?E=NB:9

4 5 2 % @66: ' 2DC:96 \$6ID ' '6 @B6: - 2D@N@B6 & : >N@D #
\$6ID J G8B >C6G>H B J A@E@A: C@B: H>C>K>D >C I=: + (, B: I67DA8 E@L6N
IDH.EEGH1H BDC6: A@DL I=: ,8>+ E 9D> H

4 5 # 6 C < # %J !D B >C< -->D9DMG G9J8I6H >H>GK: G7H@NB9D>9> 7N
8JG8B >C# >DA =:B D 9D>

4 5 ! ! - [CCHC ,DA7>A>N 8= B >8A6C9 E=DID8: B>86A@H67>AND; 8JG8B >C>C
H.G686C I HAJ>D>H , I J9>:HD; 8JG8B >C6C9 8JG8B >D9H 11" "") = 6C6C>
D

4 5 9: & 6 G6A>D \$ -6 @J8=>+ & : G@9C # 9: & DJG6 & % -DG@H
)@9J8I>DC HAJ>A>N 6C9 6C>DM9C 68I>K>N D;8JG8B >C@C@H>HEC HBC DD9
,8>-: 8=CD A 6 BE>G@H D 9D> 1

4 5 # 2 06 C < & ! !)6C % =:C< % " %S 2 , !D 2 !H>=: # \$ %S
, I 67>AND; 8JG8B >C>C7J; ;G HAJ>D>H 6C9 8=6C8: G@B>DCC; >H9: <G96I>D
E@9J8I #) = 6C68: J I >DB: 9 C 6A D =IEH 9D>DG

4 5 ' : BE =6I>G , \$H>DG' \$6I6A) A7C 66C9 6<<G 6I>D 7: =6K>DCC; 8JG8B >C
>C6J: DJH7>C6N@B>MUGH D; I =6CDA + , 9 K D 9D>

4 5 - &6H6 2 -D>! 6 C9D - &6: @6L 2 -6 @96 ! 26B6<J8=> , I G8JG6A
>9C I>86I>DCC; C: L 8JG8B >C9>B: G8C9 I=: >G8DC I G7J I>DCID I=: 6C>DM9C
B: 8=6C-B H D; 8JG8B >C# < G8 DD9 =:B D =IEH
9D>DG ?; H

4 5) +: 99N , J 9=6G@>6C +6D + % @H=" C: G@I>D D; 8JG8B >C I=:
=JB6C H.G.B 6AJB>C D6 H8I I@H I@E:8 HU9N %E9H D
=IEH 9D>DG H M

4 5 , + %@A6C: ' J 7@N DA>G) DCC6 J + 6 GBC + D JADB7:
, I J C @) : 6JA>J & D C>D>G6<9G< H A; 6<<G 6I>D 6C9 ED: C I>A>DG
E@B>HJ>N>C D; I6G>I >C>K>D E=6C68DA@N@H8: CH7N 6 E@B>86A' & +
HG6<N # & : 9 =:B D =IEH 9D>DG
?B

4 5 \$JCL6G 6 G@+) 6 C9N \$ ") G>N96G16> -G6CH@D@G; %E@H6B A6C9
6AJB>C A@B9: 8JG8B >QD A@C<8: A@ 6C67H I@E@DCC9; AIDGH8C8:
H8I I@H I@E:8 HU9N >D8>B >DE=NH 8 I6 D 9D>
>776<C

4 5 \$JCL6G 6 G@ & >H6G \$) GJN696G16> \$ +6I>=>G6B N +) 6 C9N
>; : G I>6AJE I6 @:6C9; AIDGH8C8: D; 8JG8B >C6 N: A@B E>B: C I ; @B I J B: G8
>C@B6AKH J BDC8: A@ + : L HAJ: G D

4 5 - DA>G %8DA@G -6C + G>:A) AN: G /8 :A6G & &6? :9)
, DG9AD >HIG7J I>DCC; 8JG8B >C6C9 -! >CE: G6A7AD@B DCCDJ8A6 G8: A@
>@6I: 9 ; @B =: 6A=N>Q>K>J6A I6C9 E@: C IHL>=: 8=GD>8 A@B E=D8N8
AJ@B >6 C I>86C8G>: H D =IEH 9D>DG
6C86C6H

4 5 & +D I=: (7 6>96 I 6 <: C7J8 = (-) H (- H I=: D@6C8 6C>D
6C9 86I>DCI@G@H@G H@D; I=: , % (6C9 , % <: C: PHE: G6B>A>H G #
) = 6C68DA D =IEH 9D>DG ?

4 5 ' , B >E 0 ><< , E6G67DDB +DA: D I=: AK: GHEB>>8I@G@H@G GH
(-) 6C9 (-) >C>K: G6G 9G@: A>B>G I>D ME: G I>E>C G J< & : I67
-DM9DA D =IEH 9D>DG

4 5 , \$ >> <6B \$ - J H = &6GDKI H@ , 2 = C ! %J +>8=6@ /
= 6I6C:6G 0 OJ -=: D@6C8 6C>D I@G@H@G G (- , >6B>AN6 H@H@H H7>D@>N
E: G@: 8I>K = N H@A +: K D =IEH 9D>DG
E=N@K

4 5 3: @> , (I I \$ D =A =: D@6C8 6C>D I@G@H@G GEDA ME: EI>9H (-)
>C I=: BDJH A C<6C9 =JB6C 6G6L N: E>I=: A>B >BEDG6C BDA8JAG6G>I H>C
I=: 9: K: A@B: C I D; >G6A9 H6I>G@H B # +: H6G G I 6 G: & 9

4 5 1 3=DJ 3=6C< =:C 3 J D # %J # 2J 2 1J 3=DC< ! #6C<
' B E@B I D; 8JG8B >C D C I=: E=6C68D@G: I>8H D; G@N K@H6I>C>C@H6C9 9D>H
76H9 DC I=: 8DC7<6I: 9 B: I67DA' H I: C D>D>B D =IEH
9D>DG

4 5 ' #6: G6EDG< * #6B>A # +>6 & A@B6C D@G \$G I>D6 , I ><: G \$
#6G @B ? D @ 0 #>S: G (G<6C 8 6C>D I@G@H@G C<E@A ME: EI>9H D C I G J I: ID I=:
J I6 I @: D; 8JG8B >C6C9 >H B >C: I67DA' H7N =JB6C 7G6 H I86C8G8: A@ >BE@B
DC6@J B D G68I>K>N (C 8DA +: E D 9D>
DG

4 5 # J C DA>G & 6 G6J & B 69 =: AK: GE6G I>E@D; ;>8>C I
8DG@I: 9 >G>7>DGN F J D I>C I 6C9 I=: E=6C68D@G: I>8 E=6C68D@N C@B>8
G@B>D>H>E@D; 9: G8 IAN68I>C<6C>=: E@B>H K>G J H6<C I H>C>J B6 C H C I>B>8D7
<: C I H =: B D I=: G D =IEH 9D>DG

4 5 # + 0>J>C>LH>> />A9:9: 'D GTC) GIJGHG "C9:EI= FJ6C>6I>K:
606ANHH6C9 8DBE6G@D;I= =JB6C= :E6D8N: 6C9 =: E6D86 8:AA6: !: E
E6D8B: H #)GD:DB>8H D 9D> ??E8D
E J7 #6C

4 5 & 0 ,8=6:::GH%& G:H= 6GH & # C9: GBC 2 %6 G>A # 6)CN6
) # ,DJL=:GC) & ,8=A:K:G1 & %): !: GBC E>=: A6AE@C:AA6B 6IDN
GH@H: 6C9 8JG8B >C>B: 9<6:1 9 E@H18:DC;@B H6E=NA@B86AIDM8 H-D8@
HNC9GB: IDMG)%(, 9D> ?DCC6AEC:

4 5 , 6 C8A, = =7:7 G J G8B >C6@D 6C9 >C8B7>@>D>L>= 6J<B:C<C
E@H18:1H6<6<CH EJA@D@G:CA6B B61>DC6C9 68J: A.C<>CJGN: C:G 6 9 JG6<
>A HAA6E@CJ BDC@: @9J8:9 A.C<>C: 8I>D>C % 8B>8: # &: 9
&>8@D>A D =IIEH 9D>DQ ?BB

4 5 2 %6 \$JCCJB 6@66 '6 >G0 & &: G6 %2 I6 C ' GB6>O
) : C6 \$6B6I 0 ,E6CCJ=: & : GH CHDC, % \$J<:C9DG;
< <6GL6A \$,DD9 J G8B >C>G>7>HJ BDG<@L I= 6C9 6C<D<C: H>H<C
D16G<C868@B6 7N16G4 >I=: C:J8A6G:68IDC@ E@L=L6 N +>C 6 C8G+: H
D =IIEH 9D>DQ

4 5 , \$ /6 G: & \$6@66 & - +J;>C # GDL:AA) 'D GEDA: 3 ?JG<8
G:C:G) = 6@68D@G: I>8HD; 8JG8B >C8D7<6I: B: I67DA<H>C=: 6A=N
=JB6 C H J ?8IH 6 C8G E >9B >A >DB6@GHG:K D
=IIEH 9D>DQ

4 5 , ' ID := A: ;>::G & &: IOAG AJ8JGDG@>D;D; 8JG8B >D9H7N=JB6C
B>8@D@B6A6C9 G8DB7>@C.) <A8JGD@H@K6CH;G6HH & DA'J IG DD9+: H
D =IIEH 9D>DQ BC;G

4 5 6 G86 # % #D: H + >C<=: : CCHDC) 6 GBG + = 6@6
0) , !: L 6@ : # H8: G: !: I8>D; 8JG8B >C6C9 >HB: I67DA<H>C=: E@8
I>H8 6C9 EDG6A7AD D; E@>C: H; DA@L >C: D6A69B>C: HIG6DC G # 6 C8G
D 9D> H778

4 5 2 & #6 - 3=J ! 3=DJ # 3#> - 6> ! 1x & J A@GK GHH6C8:
6H@8:1 9 E@H1: >C >HGHD@H7A: DGI=: : ; AMIG@CH@D; 8JG8B >C
<A8JGDG:9 ;@B =: E6D8N: HID I=: 7AD@ GJ< &: I67 >H@H
D =IIEH 9D>DQ 9B9

4 5 \$J C>G D) % J H # G>@N # GN: ! ! , = DL ,8=C>9: G # %
J C @: !6 <A8JGDG:9H 866A@H9: 8DC7<6I>D 6C9 68K6>D; 8JG8B >C
<A8JGDG:9 >C7D: # '6 I 9D> D 9D>

4 5);>::G, " ID := A: , 06 A@ +>HH & , %D@B & &: IOAG
J G8B >D9H: DGBG68K: <A8JGDG:9H >C>K@D # < G8 DD9 =: B
D =IIEH 9D>DQ ?;

4 5 - & XG@G : E: G@G\$ - \$>K@I & 88 A: A@C) G>D G>9: A
%69G \$ DHH ! - DDB: H + >: G@HB6C ! \$ @D: B: G C=6C89 JEI6@D;
9DM@7>8< >D 7@D@>@868@D B6 p <A8JGDG:9H B: 9<6I: H GA6H D;
9DM@7>8<; @B 6 <A8JGDG:9 E@D9J ! +> 6I I=: IJBDGH# 6 C8G
+; H D

4 5 - DA<G %8DA@G -6C + G>A /8: A6G & 86?>9 %!: ABC
>HGJ I>DC6C9 B: I67DA<H>C=: E@8J8 %>@H@B6A J G8B >C>C9D 6C9
=JB6 C 7AD@ 8: A@H@B>: H H A@I>K N6C9 E=6@68D@G: I-8 GA K6C8 C I-86C8G
+; H D 9D> 6C: 86C8G

4 5 , # 3JC@D ! , D@H #0 ' LB 6C - %): 9: GH %\$: : C # & J 8D:
(G6AD@E6G C: G6A69B>C: HIG6DC; 8JG8B >C9D: H CD E@K: C I I=: <@L I= D;
=>=: GH @ 68J: A@B E=D7A@H-8 AJ@B >68: A@H C<@: I: 9 >D6 (' ,
BDJH BD9: A "C # (C8DA D 9D> >D

4 5 ,) : G@H + /: G@HNA: \$!>AA")6 GK C & = G69<AA+ , = 6@6 %
& 6@C & % 0>A@B#) 0>A@B 0) , !: L 6@ # : H8: G = : B DE@K: C>K
:: : 868N6C9 E=6@68D@G: I>8HD; 8JG8B >C>C: & < BDJH 6 BD9: AD;
>6B>A6A69: CDB6IDJHEDA@D H 6 C8G E >9B >A >DB6@GHG: K: C I
D

4 5 , >H4 & &>O.B6 : A@B6C ' (I I: C>D; , & !D C<) @6B6C@/
=: C66 \$6G@6+ , = 6@6 & D<<@H & +J9: @+ +6K> 86>G6
& 6>G6 , NHIB >869B>C: HIG6DC; E@H: G8 C6C@E6G@A: : C8E@H@6I: 9
8JG8B >C' 6D J@ 7AD@ H@B D G<@L I= 6C9 B: I6H6H >C@E@A@8@B D9: AH
D; E@C@G6I>866C8G & DA 6 C8G =: G 9D> 9D>

4 5) +6B6A6<6B 2 - \$D K6A96I: 9 % & , B: I=D9; DG' J G@>6I>K:
606ANHH: 8JG8B >C>C@B DJH E@H@B 6C9 7@C: I>H8 6C9 >H6E@A@>D>C
E=6@68D@G: I-8 6C9 7@C: 9>HGJ I>DCHU9>H # = GB6ID<G
D =IIEH 9D>DQ ??8@B7

4 5 2 06 C< J > J > 0J + 06 C< 06 C< J G8B >C@E@H18IH I=: E6C8G6H; @B
68J: E6C8G6I>H K6 I=: B>D<: C68K6: 9 E@H1: @G@H: H@G@A@E@G=L6 N
& DA &: 9 +; EI D =IIEH 9D>DQ

4 5 % !: ABC DA<G & 86?>9 /8: A6G \$ J 86? & 6I67J9A "C JH@C
E=6@68D@G: I>8HD; %>@H@B6A J G8B >C 6C9 >HB: I67DA<H>C
I: I@G=N@B@JG8B >C>C: 7<6A: 9D<H C I-86C8G+: H D
, I D@6 /8: A6G. \$>@B@8 DJN6 , 0: >H@66G, H8=6J: G
DA<G % !: ABC & 0D AD , 6: ; IN IDA: G@>A@N 6C9 E=6@68D@G: I>8HD;
A@H@B6A J G8B >C>C@E@H18IH I=: >C>: 6A=N=JB6CH "C # A>C) = 6@68DA
=: G D =IIEH 9D>DQ

4 5 % 3=DG: 6 & = >J # 06 C< 0 = : C 0 2) C 6 C ! 6 K69 2: : \$ \$
= 6C C=6C8B : C I D; 8JG8B >C@E@A67H@D@C6C9 E=6@68D@G: I>8HD;
8JG8B >D9H6C9 8JG8B >C>B: I67DA<H>C>8: 6 C8G =: B D I=: G) = 6@68DA
D 9D> H N

4 5 2 & -H6> 0 #6C = >C 0 %: % @& - ! -H6> (E I>B>H9
C6C; D@B@A6I>D DC I=: 7>D@G@87>AND; =N@E@D7>8 E@H@B = CDA8JG8B >C
>G: ANBDC<G@H DD9 =: B D =IIEH 9D>DQ
?; D@B=B

4 5 # 06 C< 1 2J % 3=6C< % 06 C< 3) : C< 2 =: C =: E=6@68D@G: I>8H6C9
I>H8 9>HGJ I>D<D; 8JG8B >C6C9 >HB: I67DA<H>C>8: >DB: 9 = GB6ID<
: =IIEH 9D>DQ 7B8

4 5 , , = >J %> & 86?>9 # \$ />H6G@I=6 +6C@C & 6>G6
) @6B6C>@# , B >H % !: ABC >::: G C I-6A9>HGJ I>D<D; >@G@C DJH8JG8B >C
>D@B@A6I>D C I=: G 7@C: C I-86C8G+: H D

4 5 86I67J9A \$ J 86? DA<G /8: A6G & 86?>9 % !: ABC >H@H
9>HGJ I>D<D; %>@H@B6A J G8B >C6C9 I: I@G=N@B@JG8B >C
>D@B@>C I L D 6C9 >C<I = DJG: C JH@D@C7: 6A: 9D<H C I-86C8G+: H
D

4 5 - DA<G %8DA@G + 6 >H6L -6C + G>A /8: A6G & 86?>9)
, DG@AD "C: CH JEI6@D: A@H@B6A J G8B >C7N@B@A@A: BN: ADB6 8: A@G: H
8DBE6G@C I D@B@A@B E=D8N: H G 9 7AD@ 8: A@H@B 8-G@D@A@B E=D8N: 8
AJ@B >68: A@H C I-86C8G+: H D =IIEH 9D>DQ
6C: 86C8G

4 5 \$ ' 6 @66L # & 3<C< , ! \$>B & # = DB6H DAG@LH@ OO->
&>N@66 & &: N@G< >::: G C I-6A8: A@H@B6A J G8B >C6C9 B: I67DA<H>D;
8JG8B >D9H>C@D@C@B: H B68@E=6<: H G <JA@DGN; : 8IH@C@E@9
688J@A@D C G # ' J IG D 9D>

4 5 \$ G8=I & ,8=S: G ! &: N: GOJ, 8=L 67: 9>H C . E I6@: I@G@H@D@G H@D;
I=: % , % 6C9 , % 6B>A@H >C6C: 86C8G I=: G@E@N BD9A@D@G H@D;
8: A@H@C I@D@C E=6@68D@G: I>8H 6 C8G H 9D>

4 5 # #6C @C & ON <6C L H @6L J6I @D L H @ : IIA@ #: A@H@6 , J G8B @6
06 I@D@H @L >I@>@L H @ , @G@B@D@#6@C@ : I: G@G@L =: !: G
8JG8B >C>: <@96I>D 8DC9: CH@D@C>H8J@6A@N>D@B@I@6I>D "C # & DA &: 9
D =IIEH 9D>DQ >B@

4 5 \$ 86G@C: H & &>8=6@G /6<: C6@H ' %@6G >) I>H &
A>@D@D@J : G@H \$ 86G@J A@H@B 7: I6 <A8JGDG:9H 68K@N 6
C@K: AID@D 9>H@G@J>H I@N E: ; @B I@N E: 6B>D@G@D: >@9J: 9 I=N@D@H@D@H
J G = N@9 # D =IIEH 9D>DQ

4 5 ! \$J=A) = 6@68DA@ND; H I@C<H6C9 E@D<H I@C: CH>@A: C8 D 9; ; G C I
GD I: H D; 69B>C: HIG6DC A>B68: G8 , J EEA D =IIEH 9D>DQ

4 5 , E: G@G. 0: G@G - & XG@G : @ @6) G>D + 06 8@ . 9 6B
& : G@C G L: ADL ! \$ @D: B: G ME@H@D@C6C9 J C8>D<D; 7: I6
<A8JGDG:9H >C@E@G@G@I>866C8G ED: C>@A@D: >C@G < I6>@ >G' 6 J@NC
, 8=B>9: 7: G@H G8=) = 6@68DA D 9D>

4 5 H -DB: = + 16 9>6@6B G> 1 3=6D GK@L D; 8JG8B >C6C9 >H9: GK@K: H
6H6C>86C8G<C I H "C # & DA, 8> D =IIEH 9D>DQ
>B@

4 5 & !) 6C - & I J 6C< # \$ % @ >D I@G@H@D@G: I>D; 8JG8B >C I=GD<=
G9J8I>D 6C9 <A8JGDG:9H >C>B>8: GJ< &: I67 >H@H D
D

4 5 - I D G6 2 6 D D G6 + J I@N@C \$6I@ =: G@E J I>8 ED: C>@D; 8JG8B
>C>C>JB6C E@D@H I: 86C8G "" J G8B >C>G>7>H@D@A; G@I>D >@J: H
6ED@D@H 6C9 >G>7>H6C<D<C: H>H D; %) E@H@I: 86C8G 8: A@H@C@K@D
) D@H I: D =IIEH 9D>DQ E@H

4 5 \$JCCJB 6@66) >6<@69?C: , J 6 : D@G@G , =: C I J
< <6GL6A, \$>H@C J G8B >C>H C H@>H = JB6C8DA@8I6A@6C8G M: C@G: I>H<C
C9: B>8: I D Y G@>6I>D 7N16G4 >C: J8A6G: 68ID@ G <JA@6 9 <C: E@D@H8I
A>C 6 C8G+: H D =IIEH 9D>DQ

4 5 6 8=B: >G : G@G & "6C8J & >A 8=A>8=G + /: CT +
>: A@K B & #D8=JB A7>C> .) ; ; ; G =: 8=B DE@K: C>K E@H@B = CDA
8JG8B >C@C: C I H=: B6ID<: C D I H76 H I86C8G B: I6H6H >C>B@J C@D: >8>C I
B>8: : A@> N@H@A >D@>: B D =IIEH 9D>DQ

4 5 ! & D<@I=69: G> ! : E=: G I I6G>D B7>@>D>D; 6@7>D>@6@86C6C9
8JG8B >C>@J: 8: H@E@D@H@H: C7G6 H I86C8G 8: A@H@C@K@D 6C9 >G>7>H@J BDG
<@L I= K6 DKG@ME@H@D@C; E AK: A>C@K@D >DB: 9) = 6@68D@G: G
D =IIEH 9D>DQ ?7>D@6

4 5) 2DNHC<D: C = >@6C6) , = 6I I6G@H@A ,) I6J@G? C I>J BDG6C9
6C>D<C<C> >868K@>H D; 8JG8B >C>C: GK@A@6C8G M: C@G: I H>C@C9: B>8:
>D@>: + "C) J 7A@H: 9 (C "6)

4 5 , >BD C I 6 G7>G) 6 A@B # 6 % @& @D & @>J I D GG6
"D D >H@H I<C<I=: G@D: 8JG8B >C>C@B D J G @D L I= 6C9 6C<D<C: H>H@C@B DJH
BD9: AD; =JB6C7G6 H I86C8G >D@>9 +: H "C 9D>

4 5) 2DNHC<D: C) 0>G6=LDC< = 6C I6B , J @6B@6C ,) I6J@G?
C I-86C8G6C9 6C9 6C<D<C>C>8: ; 8IHD; 8JG8B >C6C9 I: I@G=N@B@JG8B >C D C
>B@E@C: 9 =: E@D8: A@H@B6A J G8B >C>C9: B>8: 0D G@# 6 H@G@C: G@
D 9D>

4 5 # ! ! D C< %: ! 2 = D> ; ; 8I D; 8JG8B >C D C I=: >C: G@I>D 7: IL : : C
6C9<C<C G8: EID@C9 0C I p 86I: C@>C%) 6) M C D@G: I H \$ D G6C # . GDA
D =IIEH 9D>DQ @P

4 5 ! "C@D & (C D@G " "C@J@ & \$ J 7D6 2 \$6B696 - (H6L 6 !
\$D76N@H => 06 @6N@H => : B DE@K: C>I@D 7N8JG8B >C9JG6<I=: E@D@D@D@H
H6< D; I J BDG@: C: H@D; B6BB 6@N @C9 >C@G@>G@>9: L@I = y G@H
6 G8@D<C: H>H D =IIEH 9D>DQ 86G8C

4 5 , , 6 C8A! \$6JH6G / / 6 9=6@6B , +6KIDG #) 6C , ' +6> + J E I6
J G8B >C>B@E@C I H C D 8JG8B >C9@I >G>7>H@D<C>@J8: 9 B6BB 6@N
86G8@D<C: H>H C " G@H 6 C8G) G K +: H D =IIEH 9D>DQ
) +

4 5 # 6 G8J6'J >O+ 6 G8J6: 8:G6 ,6 CIDHJ :K6H # +6BUGO'6 K6
&DGAH J 696G666 ' R G9C6H(8 =D6 & ; : <DK6 &: C9D6 !)G69D 6 G86
(G96O+DH6D K>A (ABDH(GI>O, %VE:O>HGGDH %666 % U6O
,NC:G=H8 6CQJJBDDG=: C8 68J>KND: 86A8IG6A>I= 8JG8B >CDGGHK6GID>H
B: 9:6I: 9 7N6C<D<C: H>G>7>D>C>G:G: C: <6I>K: 7G6 HI86C8GM:CD:G: IH
6 C8GH =IIEH 9D>DG 86C8GH

4 5 #! ID C< \$, = C 6: , # :DC! 2 = D>=: ; ; : IHHD; 8JG8B >DCDI=:
>G6H: C: HHD; E6H6I: 86C8Gin vitro 6C9 in vivo)GDH6I: 6 C8G)GDH6I>8 >H
D =IIEH 9D>DG H7E86C

4 5 & %>3 3=6C< %!>AA! O6 C<! + 3=6C< J G8B >C 6 9>I 6CQ
8DBEDCC! =6H6C!>86C8G 8=>B DHC:H>O6>DC 6C9 G9>DHC:H>O6>DC: ; ; 8IH7N
9DLC G<JA6C<I=: & & D6D: C: I=GD<=: I=:)" B- (+ - , E6=L6 N
6 C8G+: H D 9D>D

4 5 &): G9 & : B: JA +: <C>6 + & DJB 9>6C + : AK: 6J J G8B >C
>G>7>HIJBDG<DLI= 6C9 6C<D<C: H>H>C>A>7A6HDB6 MCD:G: IH & DA' J IG
DD9+: H D =IIEH 9D>DG BC;G

4 5 3=J * ,=: C6 ! #>C6 (#6 %3=J %3=6C<6 J G8B >C>G>7>I 9=:
<DLI= 6C9 >G6H6C: =JB6 CBDDC8N>8 AJ6G: B>6 ! " 8: A>C>K>D7N
6A: G6<&) \$ 6C9 &&) H<6C6A<G <=: 6C68: JI >DA D =IIEH
9D>DG

4 5 + + 6A6: 0 ! -6A7 , #, =76>A DB7>G>I>D; B: I; D6>C6C9 8JG8B >C
I6Gd H7G6 HI86C8G>C>B>8: 7N6C<D<C: H>H>C>A>7A6HDB6 MCD:G: IH & DA' J IG
BD9JA6C6C9 >GJ8I>D; E >G: E: C9C1 6EDBDH>=: G 9 K &: 9 (C 8DA
D =IIEH 9D>DG

4 5) +6C6C & J @G? %! : ABC + J E16 # \$ />H46C6=6 ; ;>88ND;
AEDH66A8JG8B >C>C6 =JB6 C E6C8G6I>8JBDGM:CD:G: = BD9: A>G>7>D>C<;
IJBDDG<DLI= 6C9 6C<D<C: H>H>C>A>7A6HDB6 MCD:G: IH & DA' J IG
D =IIEH 9D>DG

4 5 # + -H6:) %>3 2 ! =: C , ! , =6=IL 6 = DJ 2 # =: C< 2 # IL 6C<
" 0 = DG: J G8B >C>G>7>H6C: HE6A8: A>A: C<86C8G8: A>H: I6H6I>H=GD<=
I=: 69>D6C8I>C' ũ7 &&)H H<6A<G <=: 6C68: JI >DA D =IIEH
9D>DG ?DCC6AEDC:

4 5 , 2VAB6O! QA: G- GI: @G ! 26N & '>H6G^ AE6 ' 8: G
"OK: H>6I>G: I=: 6C>IJBDG6: ; ; 8I D; 8JG8B >DCDI=: B>8: >CL=>8: =GA8-
6H6: H6C9 HDA9 IJBDG>H6G6I: 9 "G6C# 6 H8 &: 9 ,8> D =IIEH
9D>DG >7B H

4 5 - (\$=DG2 , \$: JB 0 %6 # ! \$>B + IJ ,=: C 1J
DE6A6G6C +: 99N 1 3=: C< < DCCN ' - \$DC< DB7>C9
>G>7>DGN; ; ; 8IHD; 8JG8B >C6C9 E=: C! =N>D>D>8N6C8: DCI=: <DLI= D;
=JB6 C) E6H6I: M: CD:G: IH>C>BBJ CD9: ;>8>C1 B>8: 6 C8G+: H
D =IIEH 9D>DG

4 5 0 3=6C< - J > %>3 * 0J % , J C %> 06 C< D C< "B E6I<G 6C>
IJBDDG68I>K>N D; 8JG8B >C7N EDAI8: G9 B>8: A>H >C I=: GBDH: CH>K =N9D<A
HNIIB >C8DA>8I6AE: GHD: 6A86G8DB6I D H6D9: A# >DB: 9 '6 CD: 8=CDA
D =IIEH 9D>DG ?7C

4 5 * 6 > 3=DJ % 1J 1 ,DC< J G8B >C6AK6I: H G=J B6I D>96G=GbH
>GJ8: 9 >C6B B6I>DC6C9 HNDK6A=: NE: G666 7N I6Gd >G B- (+ E6=L6 N>C
G6H GJ< : H>C : K: A =: G D =IIEH 9D>DG

4 5 (D C< (= &DDC & (& J C (@>\$B ! 2 2J C<! N J C = D>2 & 2J C<
&C) 6G@ 2 \$>B J G8B >C6I: CJ6I: H>C6B B6I DGNGH6D: >C% b
>GJ8: 9 =JB6 C HNDK6A: >D7A6I H6C9 8DA<C >GJ8: 9 6C=GbH>CBDJH
BD9: A "Q " BBJ CIE=6668DA D 9D>

?>CBE
4 5 , & B B6G' & 6 B: >A' , =6L N& '6 9: G D BE 66I>K
: K6A6I>DCCD; 6C>>C6B B6I DGNE6E6I>H D; I=NBDJF>CDD: 6C9 8JG8B >CJH>G
6C 6H=B6I>8 BJ G6: BD9: A "Q " BBJ CIE=6668DA D
=IIEH 9D>DG ?>CBE

4 5 & 6 3 &6 * J , & 6 J G8B >C6I: CJ6I: H 6A.G6>8>C6B B6I>DC7N
G<JA6C6C<; G<JA6C6C<; G<JA6C6C< 8: A>H - G<H =: 76A68 >C
D I6A7JB>C H: CH>D B>8: >DI: G66 D =IIEH 9D>DG
?:>DI:

4 5) 6G9> & 6 D - % C C H &) 6 <6C D + 0 =: DBEHD C (G6A
69B>C>H6C6C<; 9>: G A I M: I =6C 8JG8B >C HEEGHHHE6C>A6B 6I DQ
8ND@G: H6C9 9: HG 8I>K 8DCC8I>K: I>H H GBD9: AS<>CME: GB: C I6A
679DB>C6A6DG>86CJ GNIIB C C /6 H8A6G, J G< D =IIEH
9D>DG H

4 5 - ! =: C 2 26C< # 06 C< # 06 C< J G8B >CIG6I B: C I E6I 8IH
6<6C H G C 6>A>B>B >66C9 GE: GJH>D>C>GJN>GJ8: 9 86C9 9N H J C 8I>6 C9
BND86G>6A>C>JGN>G6CH A) GD8 D =IIEH 9D>DG
?I6CH68B: 9

4 5 , \$=69@6, (B JG6 , 6I D \$ '>H=>D! \$6@N6 ' -HJCD96 J G8B >Cp
<A8JGDG>9 BD9JA6C H6C6IJD>BBJ C: BD9: AD; BJ A>A: H A G B H L>I =: 6A G9
<J I B>8D7>D6 >C I=: >A B 6C9 ; ; 8: H GDC : AA' C: 8I &>8D7>DA
9D> ; 8>B7

4 5 + + , 8=JA! +! !D (G<6C8 6C>D I G6H6C6C< EDAI8: EI>9H : B : C<G6A H
>C86C8GE=6668DA8N & DA) = 6668DA D =IIEH 9D>DG
BDA

4 5 " C I J C: H ! # !>B6) ! AHS<6 / > >6A D6G6D K6C 06 6G:
& & 0>A6 H C + >: C66 # 9: /G>H "C9J8I>D; D; p <A8JGDG>6H
GA6H 7N 8NDH6I>86<C I H>CHB6A J BDGH6DA) = 66 D
=IIEH 9D>DG BE L

4 5 * , => + !6 : C C % & 66H / & 9AI , E>G 2 + /6 H B: O & DDCC
) : >H # /6 C, 8=DD: C + 0 % D 9H6=6A "C, 6B B6I>DC6I H 6I: 9
) : M I G 6 A A A 6 6 6 < A 8 J C D G 6 H 6 A G H 6 A A 6 G G H 6 D G H I D I =: 8 = B > 6 A 8 6 8 6 D < C
7: C D M 6 E N G C: G8 = -DM8DA D =IIEH 9D>DG
H

4 5 + % 9 L6 G9H) %>3 H) / /6 G D 6 " # D H E = , !) G H A N + = 6 I J K : 9>
, 8=C>9: G =: 6C>>C6B B6I DGNGH6D: 8JG8B >C>H: 9: 6I: 9 7N>H
D M 6 I >K B: I 67DAI>H # >DA =: B D 9D>
?78 +

4 5 \$G6>@N6C' ; C I = A - &>C '6 CDJG8B >C 6 EDB>H6: 86C9>6I: ; DG
I=: G6EJ I 8 6EEA6I>D H GDC) = 6668DA 9D>

4 5 \$ & 6 C H D J G , + 6 H D A E D G 6 C: H = @ 6 = , 7 D 6 I = > ' , 6 A 6 > &
& D = 6 B B 6 9 > , + 6 H D A E D G , = 676C> A>G6A; ; ; 8IHD; 8JG8B >C>C C = 6C8>G
86C8GI=: G6EN 6 HNIIB 6I>8GK>L & 6 C8G =IIEH 9D>DG
H

4 5 & % < <6G6A \$ & = 68@D - \$ J G K A A , NHIIB 6I>86C9 8DBEG=: CHK
>G: H>6I>D; I=: ID M 8 I N D; 8JG8B >D 9 6 H H C I > 6 A D A 8 B E A M 6 7>D 6 6 A 7 A:
I J G B G 8 ; D G B J A I > D & D A & : 9 + : E D 9D>
B B G

4 5 J G D H D G D # & 6 A 9 C D C D C I 6 C D # , 6 A I 6 9 D G + D 7 A H & % I E: O
& 6 6 D =: 96G@H9: D; 8JG8B >C "Q # 6 C8G D 9D>
>8

