GPPAD-POInT Study: Visit-schedule (Study Flow Chart)

POInT Trial	**Trial**												
	Screening Phase	**Intervention**											
Visits		baseline visit (age 4 - 7 months)	visit 2 months post baseline	visit 4 months post baseline	visit 8 months post baseline	call	visit at age 1.5 years	call	visit at age 2.0 years	call	visit at age 2.5 years	call	visit at age 3.0 years
Visit window	below 7 months of age		± 10d	± 10d	± 10d		± 10d		± 14d		± 14d		± 14d
Study visit	0	1	2	3	4		5		6		7		8
Study call						1		2		3		4	
Informed consent	X*	X											
Review Incl./Excl. Criteria	X	X											
Randomization		X											
Medical History		X											
Psychological impact Questionnaire (mother&father)				X			X						X
Antibodies measurement (IAA; GADA; IA-2A; ZnT8RA; ZnT8WA; TS7A)		X	X	X	X		X		X		X		X
Vitamin D (25OHD) [B]		X	X	X	X		X		X		X		X
Intervention													
dispense medication (+ compliance data sheet)dispense medication (+ compliance data sheet)		X	X	X	X		X		X		X		
Treatment		daily with 7,5 mg Insulin OR Placebo	daily with 22,5 mg Insulin OR Placebo	daily with 67,5 mg Insulin OR Placebo									
Investigations													
Physical examination (height, weight)		X	X	X	X		X		X		X		X
Assessment of AEs and SAEs [E]		X	X	X	X		X		X		X		X[E]
Blood glucose (0/30/60/120) [C]		X	X	X	X								
Blood glucose							X		X		X		(X)[A]
Differential blood count		X[F]											X
OGTT (0/30/60/90/120) [D]													X[D]
blood volumes for protocol parameters (mL):		5.0	3.8	3.8	3.8		3.8		3.8		3.8		5-11
blood volumes for protocol parameters (%):		0.8-1.0	0.5-0.6	0.5-0.6	0.4-0.5		0.4		0.4		0.3		0.4-0.9
additional biobank blood volumes (mL):		7.5	10.1	10.1	17.6		17.6		22.5		17.6		17.6-22.5
Total blood volumes (mL):		**12.5**	**13.9**	**13.9**	**21.4**		**21.4**		**26.3**		**21.4**		**27.5-28.6**
Total blood volume (%)*:		**1.9-2.4**	**2.0-2.2**	**1.8-2.0**	**2.5-2.8**		**2.4**		**2.7**		**2.0**		**2.3-2.4**

* Start of Informed consent process

[A] In autoantibody positive children who will have an OGTT, a separate blood glucose sample is **not** taken.

[B] Measurement of Vitamin D level is recommended at each visit however a single missing vitamin D value will not be considered as protocol violation.
If a vitamin D level < 75 nmol/L will be assessed during intervention, family pediatrician will be advised to supplement patient with 1000 IU vitamin D daily

[C] Blood glucose measurements before (0) and 30, 60, 90 and 120 min after administration of the study drug (oral insulin or placebo). Single missing glucose values will not be considered as protocol violation as long as at least 2 of 4 values after administration of study drug and the value before administration of study drug are available.

[D] If the participant developed beta-cell-autoantibodies during trial. OGTT (0/30/60/90/120) will be performed and samples measured in laboratory
Children who seroconverted to beta-cell-autoantibodies should have a confirmation sample within 4 – 12 weeks (interim visit)

[E] AEs/SAEs/SUSARs will be noted and reported as under intervention phase for 60 days after end of treatment day

[F] Differential blood count may be postponed to another visit within the first year, if it's not possible to collect enough blood for all assessments at baseline. Single missing blood count parameters (except leucocytes and hemoglobine) will not be considered as protocol violation

*Blood volumes are < 5% NIH/WHO allowance and in accorance to the Pre-POINT, Pre-POINT Early and Fr1da-Intervention studies

GPPAD-POInT Study: Visit-schedule (Study Flow Chart)-version 23.11.2017

POInT Trial	**Trial**																	
	Follow-up																	
	minimum 6 months FU		**variable with maximum up to 54 months FU**															
Visits	call	visit at age 3.5 years	call	visit at age 4.0 years	call	visit at age 4.5 years	call	visit at age 5.0 years	call	visit at age 5.5 years	call	visit at age 6.0 years	call	visit at age 6.5 years	call	visit at age 7.0 years	call	visit at age 7.5 years
Visit window		± 30d		± 30d		± 30d		± 30d		± 30d		± 30d		± 30d		± 30d		± 30d
Study visit		9		10		11		12		13		14		15		16		17
Study call	5		6		7		8		9		10		11		12		13	
Informed consent																		
Review Incl./Excl. Criteria																		
Randomization																		
Medical History																		
Psychological impact Questionnaire (mother&father)		(X)[F]		(X)[F]		(X)[F]		(X)[F]		(X)[F]		(X)[F]		(X)[F]		(X)[F]		(X)[F]
Antibodies measurement (IAA; GADA; IA-2A; ZnT8RA; ZnT8WA; TS7A)		X		X		X		X		X		X		X		X		X
Vitamin D (25OHD) [B]																		
Intervention																		
dispense medication (+ compliance data sheet)																		
Treatment																		
Investigations																		
Physical examination (height, weight)		X		X		X		X		X		X		X		X		X
Blood glucose (0/30/60/120) [C]																		
Blood glucose		(X)[A]		(X)[A]		(X)[A]		(X)[A]		(X)[A]		(X)[A]		(X)[A]		(X)[A]		(X)[A]
Differential blood count																		
OGTT (0/30/60/90/120) [D]		X[D]		X[D]		X[D]		X[D]		X[D]		X[D]		X[D]		X[D]		X[D]
blood volumes for protocol parameters (mL):		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8		3.8-9.8
blood volumes for protocol parameters (%):		0.3-0.8		0.3-0.7		0.3-0.7		0.3-0.6		0.2-0.6		0.2-0.6		0.2-0.5		0.2-0.5		0.2-0.5
additional biobank blood volumes (mL):		25.1		25.1		25.1		30		30		30		30		30		30
Total blood volumes (mL):		**28.9-34.9**		**28.9-34.9**		**28.9-34.9**		**33.8-39.8**		**33.8-39.8**		**33.8-39.8**		**33.8-39.8**		**33.8-39.8**		**33.8-39.8**
Total blood volumes (%)*:		**2.5-3.0**		**2.1-2.6**		**2.1-2.6**		**2.2-2.6**		**2.2-2.6**		**2.0-2.3**		**2.0-2.3**		**1.7-2.0**		**1.7-2.0**

[A] In autoantibody positive children who will have an OGTT, a separate blood glucose sample is **not** taken.

[B] If a vitamin D level < 75 nmol/L will be assessed during intervention, family pediatrician will be advised to supplement patient with 1000 IU vitamin D daily

[C] Blood glucose measurements before (0) and 30, 60 and 120 min after administration of the study drug (oral insulin or placebo)

[D] If the participant developed beta-cell-autoantibodies during trial. OGTT (0/30/60/90/120) will be performed and samples measured in laboratory
Children who seroconverted to beta-cell-autoantibodies should have a confirmation sample within 4 – 12 weeks (interim visit)

[F] hand out of the Psychological Impact Questionnaire only if this visit is childs last follow-up visit (i.e. only at End of Study Visit)

*Blood volumes are < 5% NIH/WHO allowance and in accorance to the Pre-POINT, Pre-POINT Early and Fr1da-Intervention studies