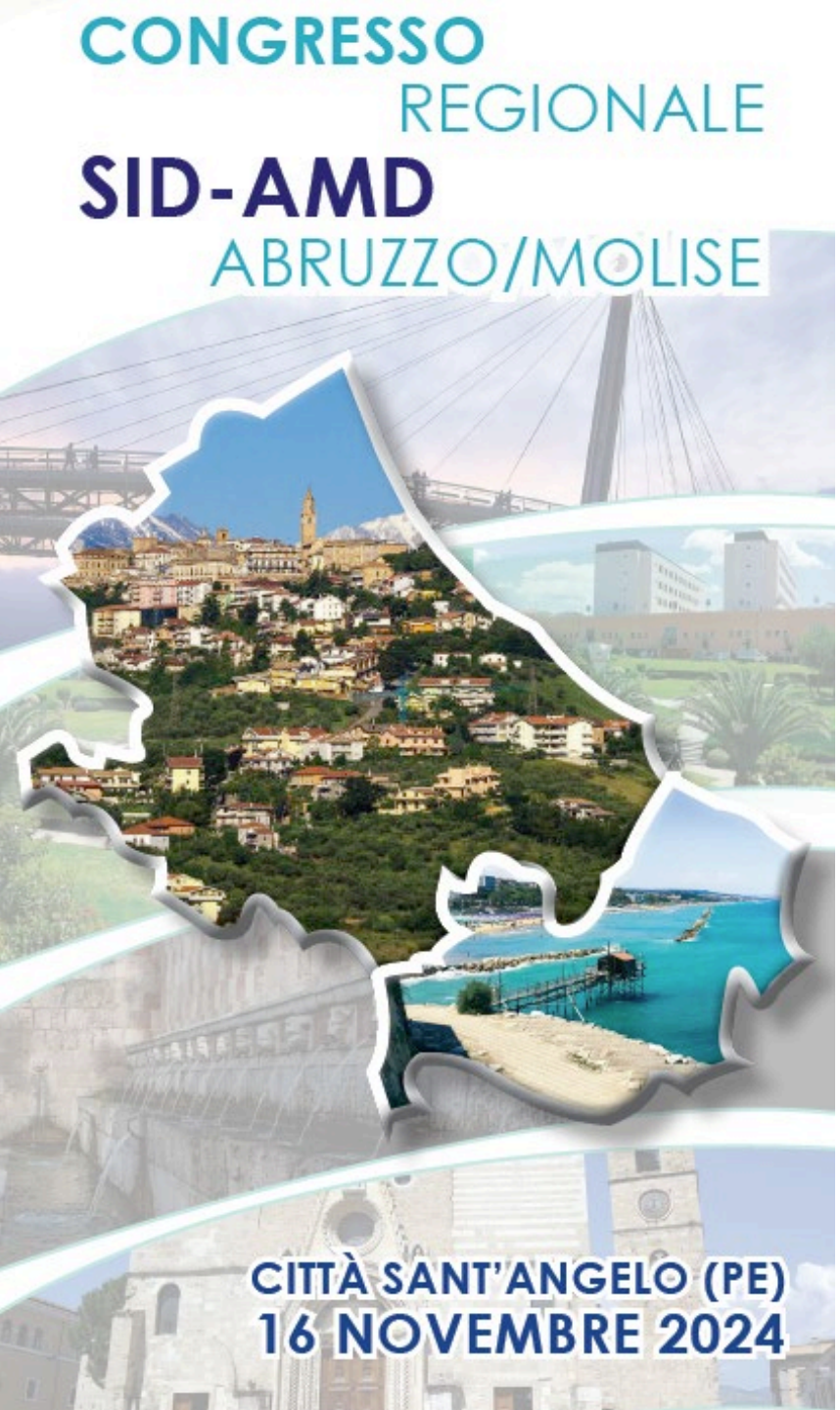


Diabete tipo 1, l'esordio può attendere: screening, tracciamento e... Prevenzione?

FEDERICA CARRIERI MD, PHD STUDENT

UOC ENDOCRINOLOGIA E MALATTIE METABOLICHE,
ASL PESCARA

DIPARTIMENTO DI MEDICINA E SCIENZE DELL'INVECCHIAMENTO,
UNIVERSITA' G. D'ANNUNZIO, CHIETI-PESCARA

federica.carrieri@phd.unich.it

La dr.ssa Carrieri Federica dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

DM1: l’esordio può attendere

Screening

Prevenzione

Tracciamento

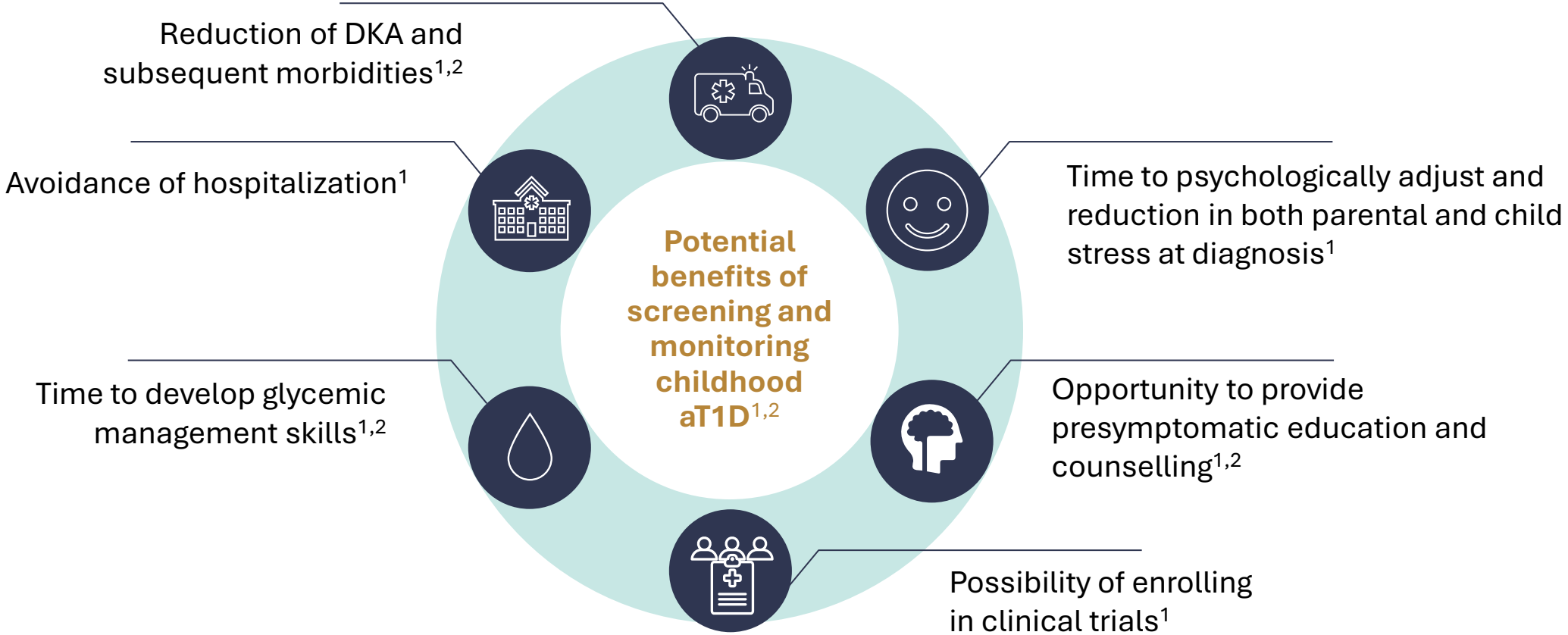
DM1: l’esordio può attendere

Screening

Prevenzione

Tracciamento

Potential Benefits of Identifying People with Presymptomatic Autoimmune T1D[1,2]

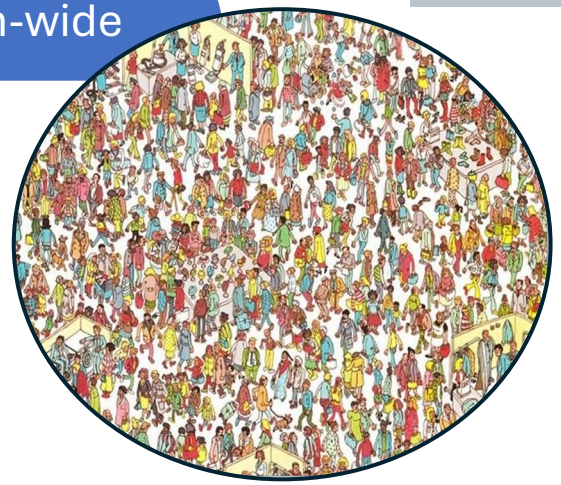


aT1D, autoimmune type 1 diabetes; DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

1. Besser REJ, et al. Archives of Disease in Childhood. 2022;107:790-5. 2. Scheiner G, et al. ADCES in Practice. 2022;10(5):20-5.

WHO?

population-wide



first-degree family members

- Only ~10% of people with T1D have a first-degree relative with T1D

- The rate of disease progression, once Stage 1 diabetes is confirmed, is not significantly different between individuals with a family member compared to the general population

- DKA rates are lower in individuals with a first-degree relative of T1D

ISPAD clinical practice consensus guidelines 2022: Stages of type 1 diabetes in children and adolescents 2022

HOW?

Screening for the Presence of ≥2 Islet Autoantibodies Can Identify People with Presymptomatic Autoimmune T1D (Stage 1 and 2)[1,2]

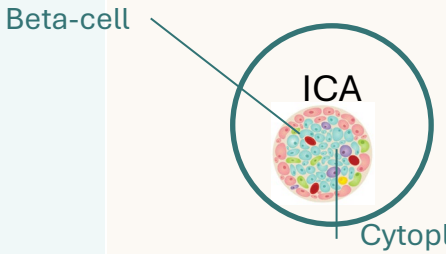
There are five primary islet autoantibodies, against:[1,2]

Insulinoma-associated antigen-2

Glutamic acid decarboxylase

Zinc-transporter 8

Non-specific target[1,2]



Islet cell

A combination of these four primary autoantibodies are typically screened for aT1D[1,3]

Not recommended for routine testing: ICAs are highly indicative of beta cell injury but have many target molecules and therefore lack sensitivity.[1,3,5]

The presence of autoantibodies alongside metabolic status define the three Stages of aT1D[4]

aT1D, autoimmune type 1 diabetes; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; IAA, insulin autoantibodies; ICAs, islet cell cytoplasmic autoantibodies; T1D, type 1 diabetes; ZnT8, zinc-transporter 8.

1. Winter WE, et al. J Appl Lab Med 2022;7:197-205. 2. Bonifacio E, Achenbach P. Clin Exp Immunol. 2019;198(3):294-305. 3. Peters A. J Fam Pract 2021;20; Suppl:S47-S52. 4. Insel RA, et al. Diabetes Care. 2015;38(10):1964-74. 5. Simmons KM, Steck AK. AACC 2017. Accessed May, 2024. https://www.aacc.org/cln/articles/2017/july/islet-autoantibody-testing-predictingand-diagnosing-type-1-diabetes .

Which Population Are We Targeting?

GENETIC RISK

Starting Point

IMMUNE ACTIVATION

Trigger Event
Development of single autoantibody

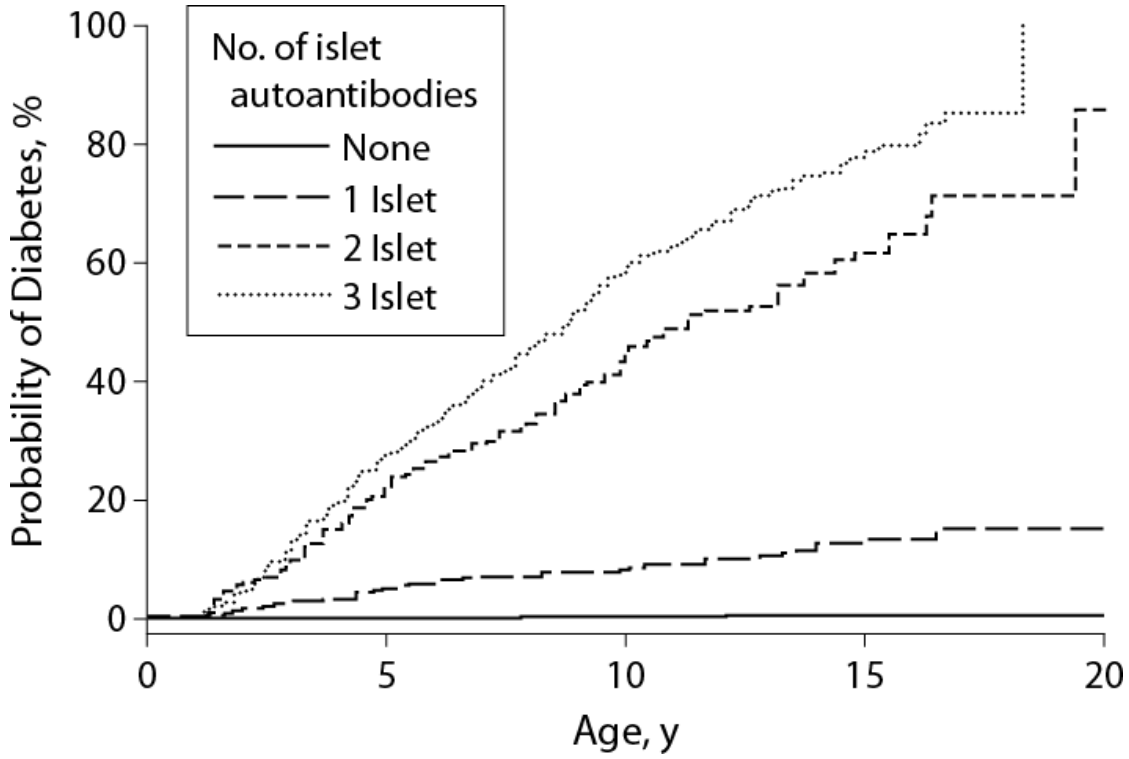
	STAGE 1	STAGE 2	STAGE 3	STAGE 4
	Normal Blood Sugar ≥ 2 autoantibodies	**Abnormal Blood Sugar** ≥ 2 autoantibodies + dysglycemia	**Clinical Diagnosis** Based on ADA criteria for diagnosis of diabetes At the time of diagnosis, there is still □-cell reserve with clinical significance in terms of glycemic control and avoidance of hypoglycemia	**>Established T1D** Cell function continues to decline with time after diagnosis
Pathophysiology:	Identifies individuals who have developed a broad autoimmune response against multiple islet autoantigens and will eventually progress to clinical disease	Cell dysfunction, defined based on dysglycemia, can be identified using provocative testing (e.g., oral glucose tolerance tests)		
5-year risk of clinical diagnosis of T1D:	**44%**	**75%**	N/A	N/A

Sims EK, et. al. Diabetes 2022;71:610–3; Besser RE, et al. Pediatr Diabetes 2022;23:1175–87

Biomarkers for an early diagnosis

Risk of progression to symptomatic type 1 diabetes with **multiple islet autoantibodies** approaches 100%

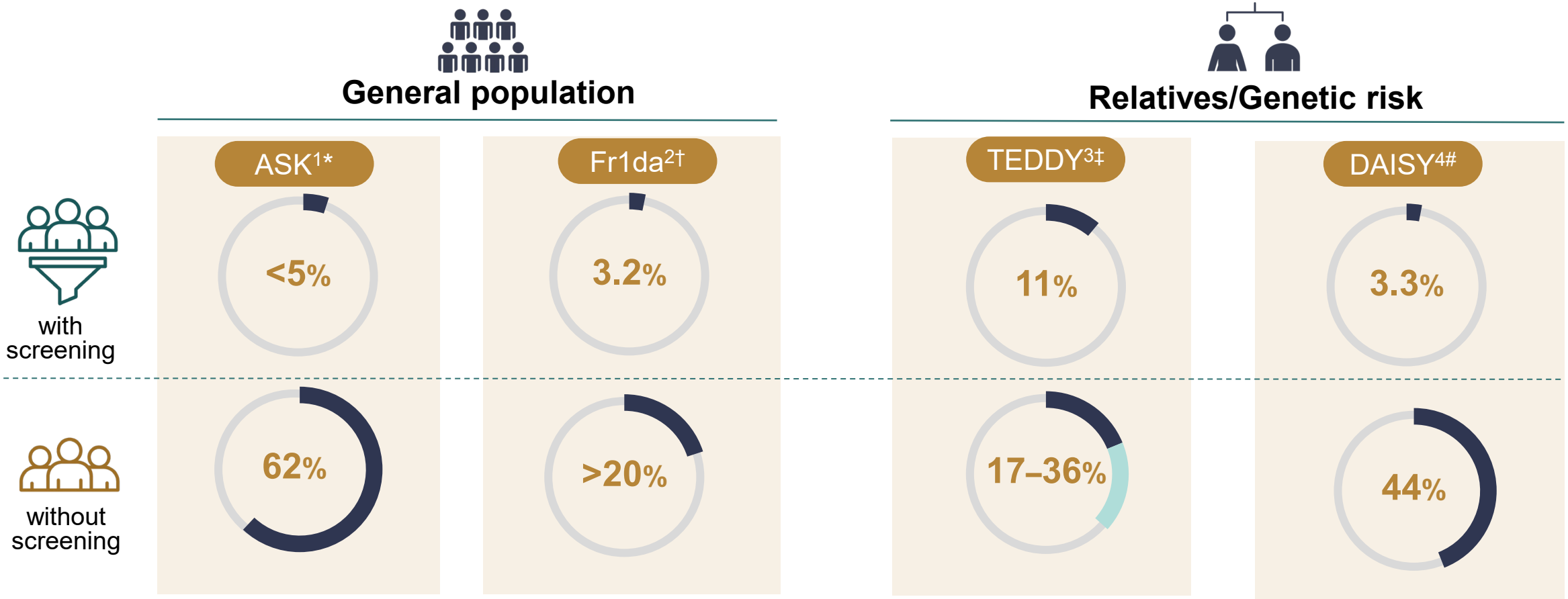
General population



paradigm shift for staging of type 1 diabetes before clinical onset

Ziegler AG et al. JAMA 2013.

Autoimmune T1D Screening Is Associated with Lower Rates of DKA at Diagnosis[1-4]



*ASK screened >32,000 children in Colorado (US) for islet autoantibodies and found a 1% prevalence of presymptomatic autoimmune T1D.[1†] Fr1da screened 90,632 children in Germany for islet autoantibodies. A total of 280 children had presymptomatic autoimmune T1D.[2] ‡TEDDY screened 424,788 children for autoimmune T1D HLA risk at birth in the US and Europe and enrolled 8677 children. Of those, 79 aged <5 years were diagnosed with autoimmune T1D during follow-up.[3] # DAISY was a prospective study in Colorado (US) following infants carrying genotypes associated with autoimmune T1D from birth. Of the 2157 enrolled, 30 participants have progressed to autoimmune T1D. Hospitalization rate, mainly driven by DKA in the control group was reported rather than DKA.[4]

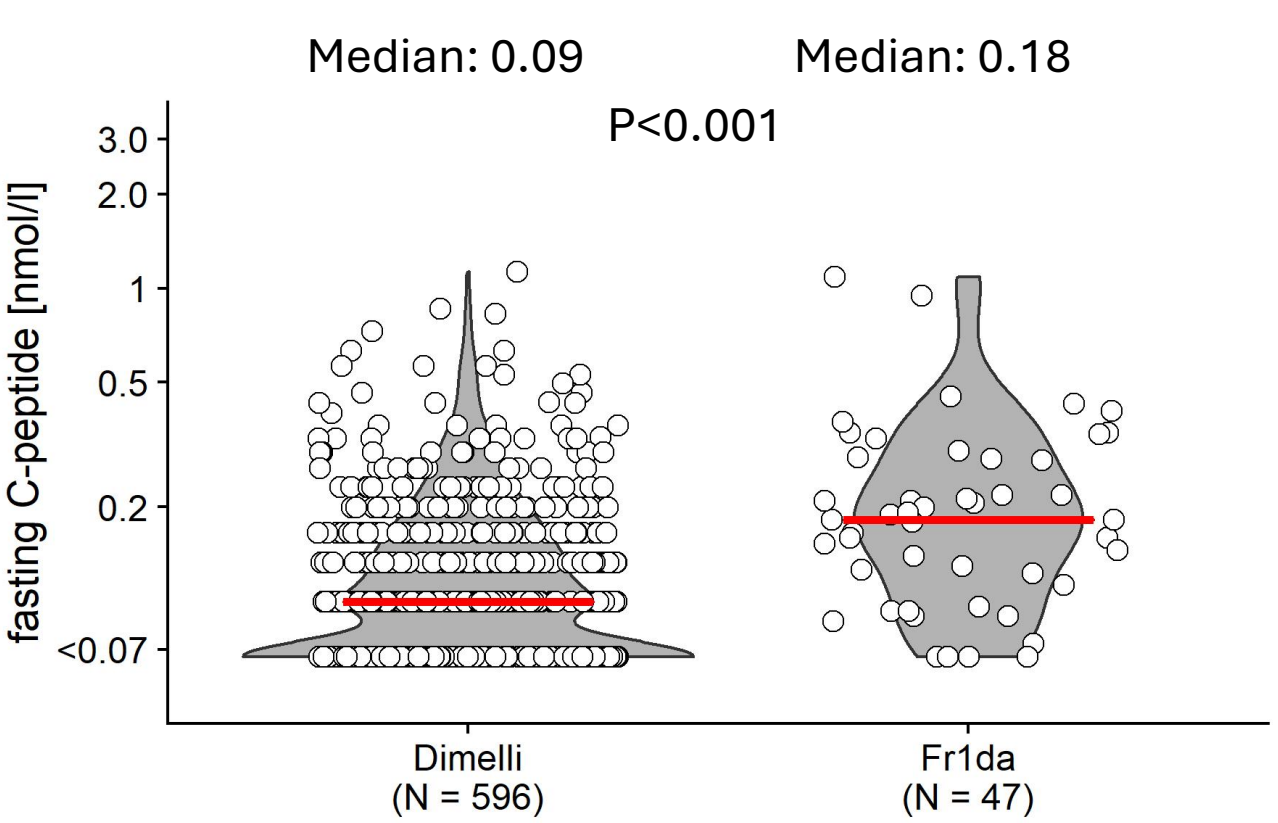
ASK, Autoimmunity Screening for Kids; DAISY, Diabetes Autoimmunity Study in the Young; DKA, diabetic ketoacidosis; HLA, human leukocyte antigen; T1D, type 1 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young.

1. diaTribe. https://diatribe.org/early-diabetes-screening-kids-can-improve-quality-life. Accessed July 2024. 2. Ziegler AG, et al. JAMA. 2020;323:339-51. 3. Larsson HE, et al. Diabetes Care. 2011;34(11):2347-52. 4. Barker JM, et al. Diabetes Care. 2004;27(6):1399-404.

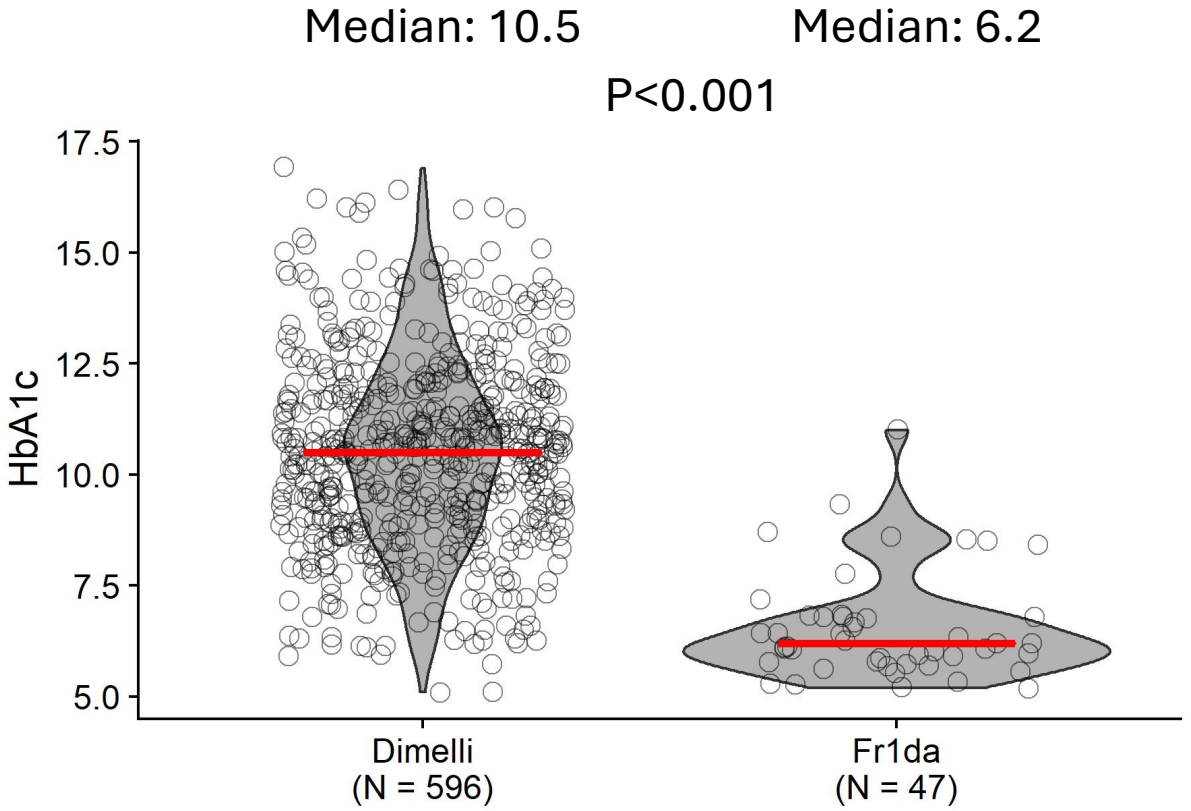
Better preservation of residual β-cell function and milder clinical presentation

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Fasting C-Peptide at clinical manifestation



HbA1c at clinical manifestation



DiMelli
Studie zur Untersuchung von neu aufgetretenem Diabetes mellitus im Kindes- und Jugendalter

New onset register cohort in children in Bavaria, Germany

Hummel S et al. Diabetologia. 2023 Sep;66(9):1633-1642

Legge 15 settembre 2023, n. 130

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 164° - Numero 226

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Mercoledì, 27 settembre 2023 — SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA
AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - VIA SALARIA, 691 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO PIAZZA G. VERDI, 1 - 00198 ROMA

La **Gazzetta Ufficiale, Parte Prima,** *oltre alla* **Serie Generale**, *pubblica cinque Serie speciali, ciascuna contraddistinta da autonoma numerazione:*
1ª Serie speciale: *Corte costituzionale (pubblicata il mercoledì)*
2ª Serie speciale: *Unione europea (pubblicata il lunedì e il giovedì)*
3ª Serie speciale: *Regioni (pubblicata il sabato)*
4ª Serie speciale: *Concorsi ed esami (pubblicata il martedì e il venerdì)*
5ª Serie speciale: *Contratti pubblici (pubblicata il lunedì, il mercoledì e il venerdì)*
La **Gazzetta Ufficiale, Parte Seconda,** "Foglio delle inserzioni", *è pubblicata il martedì, il giovedì e il sabato*

AVVISO ALLE AMMINISTRAZIONI

Al fine di ottimizzare la procedura di pubblicazione degli atti in *Gazzetta Ufficiale*, le Amministrazioni sono pregate di inviare, contemporaneamente e parallelamente alla trasmissione su carta, come da norma, anche copia telematica dei medesimi (in formato word) al seguente indirizzo di posta elettronica certificata: gazzettaufficiale@giustiziacert.it, curando che, nella nota cartacea di trasmissione, siano chiaramente riportati gli estremi dell'invio telematico (mittente, oggetto e data).

Nel caso non si disponga ancora di PEC, e fino all'adozione della stessa, sarà possibile trasmettere gli atti a: gazzettaufficiale@giustizia.it

SOMMARIO

LEGGE 15 settembre 2023, n. **130**.

Disposizioni concernenti la definizione di un programma diagnostico per l'individuazione del diabete di tipo 1 e della celiachia nella popolazione pediatrica. (23G00140) . . . . . *Pag.* 1

IL PRESIDENTE DELLA REPUBBLICA

Promulga

la seguente legge:

Art. 1

Programma di screening nazionale
per diabete di tipo 1 e celiachia

1. Al fine di prevenire l'insorgenza di chetoacidosi in soggetti affetti da diabete di tipo 1 e di rallentare la progressione della malattia mediante l'impiego delle terapie disponibili, nonché di effettuare la diagnosi precoce della celiachia, con decreto del Ministro della salute, da emanare entro centoventi giorni dalla data di entrata in vigore della presente legge, previo parere della

DM1: l’esordio può attendere

Screening

Prevenzione

Tracciamento

D1Ce Screen

D1Ce Screen

PILOT PROGRAM

Progetto Propedeutico per la realizzazione di un programma di screening nazionale nella popolazione pediatrica per il diabete di tipo 1 e la celiachia (D1Ce Screen)

Progetto propedeutico al programma di screening che ha lo scopo di evidenziare la sostenibilità da parte del Servizio Sanitario Nazionale, le potenzialità, le criticità organizzative e i costi-benefici di uno screening su scala nazionale per le due patologie.

Saranno **arruolati 5363 residenti in 4 regioni (Lombardia, Marche, Campania, Sardegna)** e stratificati per 3 fasce di età: 2-2.9, 6-6.9, 10-10.9 anni

Età	Lombardia	Marche	Campania	Sardegna	Totale
2	815	111	520	97	1543
6	972	134	581	123	1810
10	1080	149	638	143	2010
Totale	**2867**	**394**	**1739**	**363**	**5363**

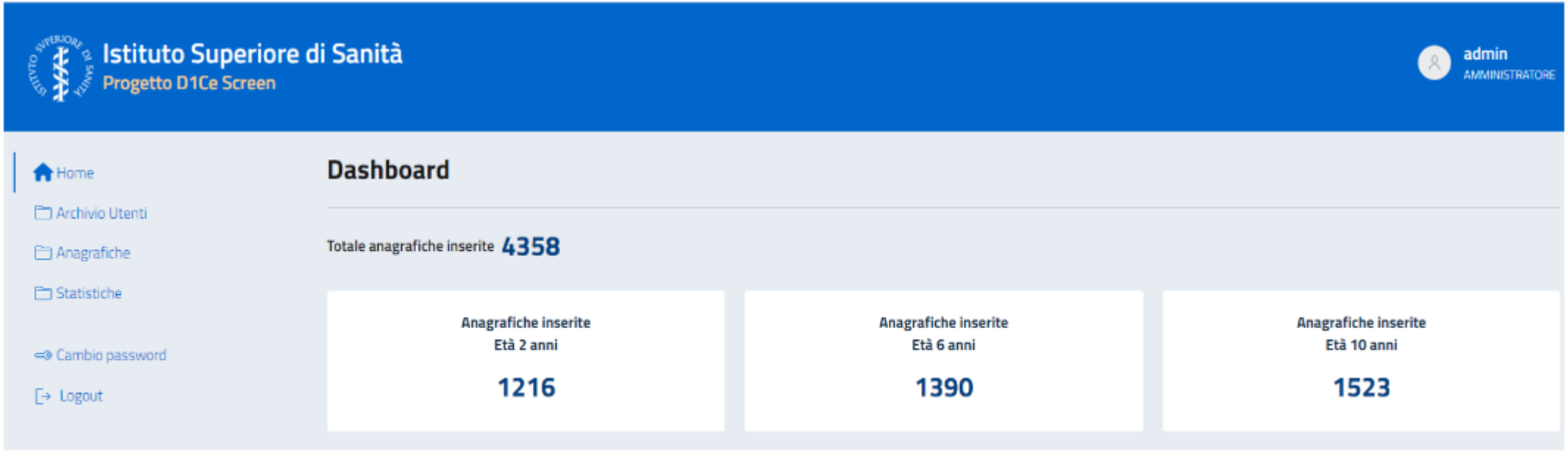
Progetto Propedeutico per la realizzazione di un programma di screening nazionale nella popolazione pediatrica per il diabete di tipo 1 e la celiachia (D1Ce Screen)

Recruitment in the study

Time of conduction:
April-November 2024

Published 24/01/2024 - Edited 11/11/2024

This section reports the enrollment in the D1Ce Screen study updated to November 11, 2024.



Criteri di inclusione

- Età 2, 6, 10 anni (+364 giorni con eventuali eccezioni su specifica richiesta dei genitori)
- Firma del consenso informato e dell'informative sulla privacy da parte dei genitori e consegna dell'assenso da parte dei bambini capaci di comprendere il contenuto

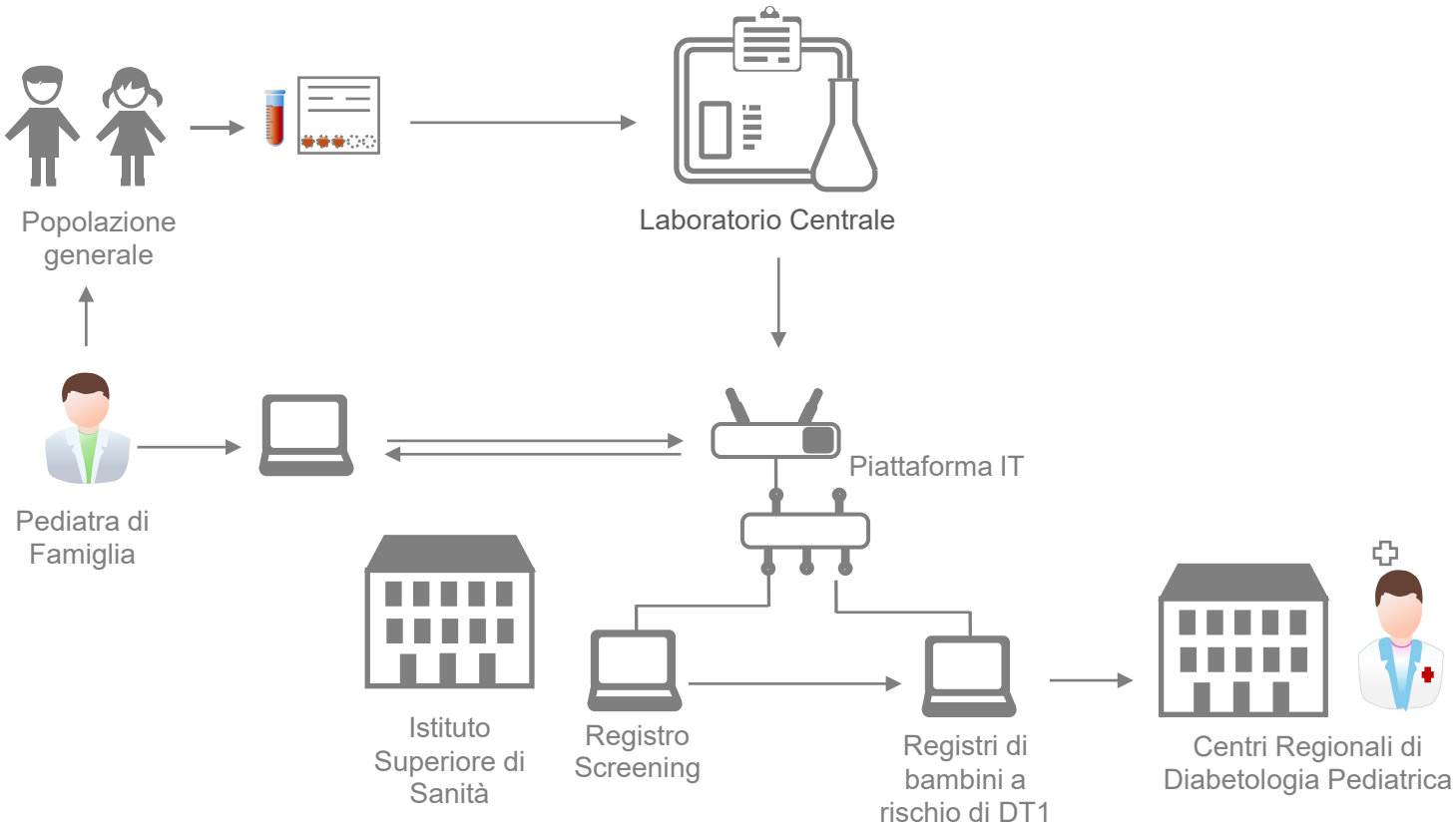
Criteri di esclusione

- Diagnosi di diabete tipo 1
- Diagosi di diabete tipo 1 e celiachia (non sono esclusi i pazienti con celiachia diagnosticata)

Dosaggi

- Su siero: 3-Screen Test (IA-2A, GADA, ZnT8A, IA) + TGA-IgA e IgG. Positivi a 3-Screen Test → LIPS
- Su cartoncino HLA DQ2-DQ8

D1Ce Screen, organizzazione generale



Monitoring and follow up may include: (under development)

- Education of T1D
- Self-monitoring capillary glucose
- HbA1c
- OGTT
- CGM
- Autoantibodies
- Psychological impact
- Anxiety and Quality of Life
- What and how frequent

Predictors of faster progression:

- Younger age
- Number of autoantibodies
- Initial dysglycemia

Cherubini, Valentino et al. “Follow-up and monitoring programme in children identified in early-stage type 1 diabetes during screening in the general population of Italy.” *Diabetes, obesity & metabolism* vol. 26,10 (2024): 4197-4202. doi:10.1111/dom.15779

National Law on screening of type 1 diabetes and celiac disease: a summary

Ministero della Salute

Sponsor

- Ministry of Health

General Objective

- Nationwide, Public Health Program in the childhood and adolescent general population (age 1-17 yr) in Italy to identify individuals at risk for type 1 diabetes and/or undiagnosed celiac disease, in order to reduce the complications associated with late diagnosis of these diseases.

Specific Aims

- Prevention of diabetic keto-acidosis (DKA) at the clinical onset of type 1 diabetes;
- Identification of pre-symptomatic type 1 diabetes suitable to disease modifying therapies.
- Prompt treatment of newly diagnosed celiac disease by gluten free diet;
- Prevention of non gastrointestinal complications of celiac disease, including impaired growth or short stature, iron deficiency, osteopenia, delayed puberty, etc.;

Comment

Screening type 1 diabetes and celiac disease by law

On Sept 17, 2023, the Italian Parliament approved with unanimous vote a law (Italian Republic Law 130/2023) introducing a nationwide screening for type 1 diabetes and coeliac disease in the general population aged 1–17 years as part of the public health program aimed at reducing the effects of these chronic diseases. This law was successfully passed because of the commitment of many people from the diabetes and scientific community and was advocated for by Fondazione Italiana Diabete.

Type 1 diabetes and coeliac disease are two distinct, but sometimes coexisting, autoimmune conditions that share some common features, including an underlying immune-mediated pathogenetic mechanism; a partially shared genetic predisposition associated with HLA polymorphisms; associations with disease-specific autoantibodies, being detectable in the circulation years before clinical onset; an identifiable long presymptomatic phase; and progression to clinical stage that can be predicted.[1,2] In addition, both conditions have continuously increased in incidence over the past five decades in high-income countries.[1,2]

There are two specific aims of the new Italian law. First is the identification of children and adolescents during the presymptomatic phase of type 1 diabetes. children and adolescents, positivity for two or more islet autoantibodies is associated with the greatest risk (almost certainty) of future disease; positivity for one autoantibody indicates an intermediate risk, and a negative autoantibody status is associated with no risk. Similarly, the development of coeliac disease—either typical or clinically silent—is associated with IgA class transglutaminase and endomysial autoantibodies that are also easily measurable and are sensitive and specific markers of the disease.[4] Type 1 diabetes and coeliac disease-specific autoantibodies can be tested together in combined screening procedures, as indicated in the new law.

Available information on presymptomatic type 1 diabetes and its natural history derives from screening programmes done in relatives or other groups of genetically predisposed individuals, for reasons of higher efficiency and feasibility. However, since most people developing type 1 diabetes have no family history, any action aiming at reducing disease burden at the public health level requires moving to screening in the general population.[5] In the general childhood and adolescent population, the prevalence of islet antibodies is around 1–2%, with 0·3–0·5% of the population deemed high risk due to having two or more autoantibodies.[6] For coeliac

studioporcobbia/Getty Images

Lancet Diabetes Endocrinol 2023
Published Online
December 1, 2023
https://doi.org/10.1016/S2213-8587(23)00354-6

For the **Italian Republic Law 130/2023** see https://www.gazzettaufficiale.it/eli/gu/2023/09/27/226/sg/pdf

Bosi E, Catassi C. Lancet Diabetes Endocrinol. 2024 Jan;12(1):12-14

DM1: l’esordio può attendere

Screening

Prevenzione

Tracciamento

DM1: l’esordio può attendere

TEPLIZUMAB approved by FDA as the first and only treatment indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adult and pediatric patients aged 8 years and older with Stage 2 T1D

November 17, 2022

Prevenzione

Autorizzazione Uso Compassionevole di Teplizumab in Italia

1 messaggio

Segreteria SID <Siditalia@siditalia.it> 29 ottobre 2024 alle ore 16:39

STADIO 2

≥ 2 autoanticorpi + disglicemia

Tale terapia potrà essere somministrata a persone di età > 8 anni, positive ad almeno due autoanticorpi associati al diabete tipo 1 e con disglicemia definita in soggetti adulti come glicemia a digiuno compresa tra 100-125 mg/dl, glicemia a 2 ore dopo carico orale di glucosio compresa tra 140-199 mg/dl e HbA1c tra 42-48 mmol/mol (6,00-6,49%) (solo dosaggio allineato con IFCC) in accordo agli Standard di Cura Italiani per la Cura del Diabete Mellito.

Teplizumab

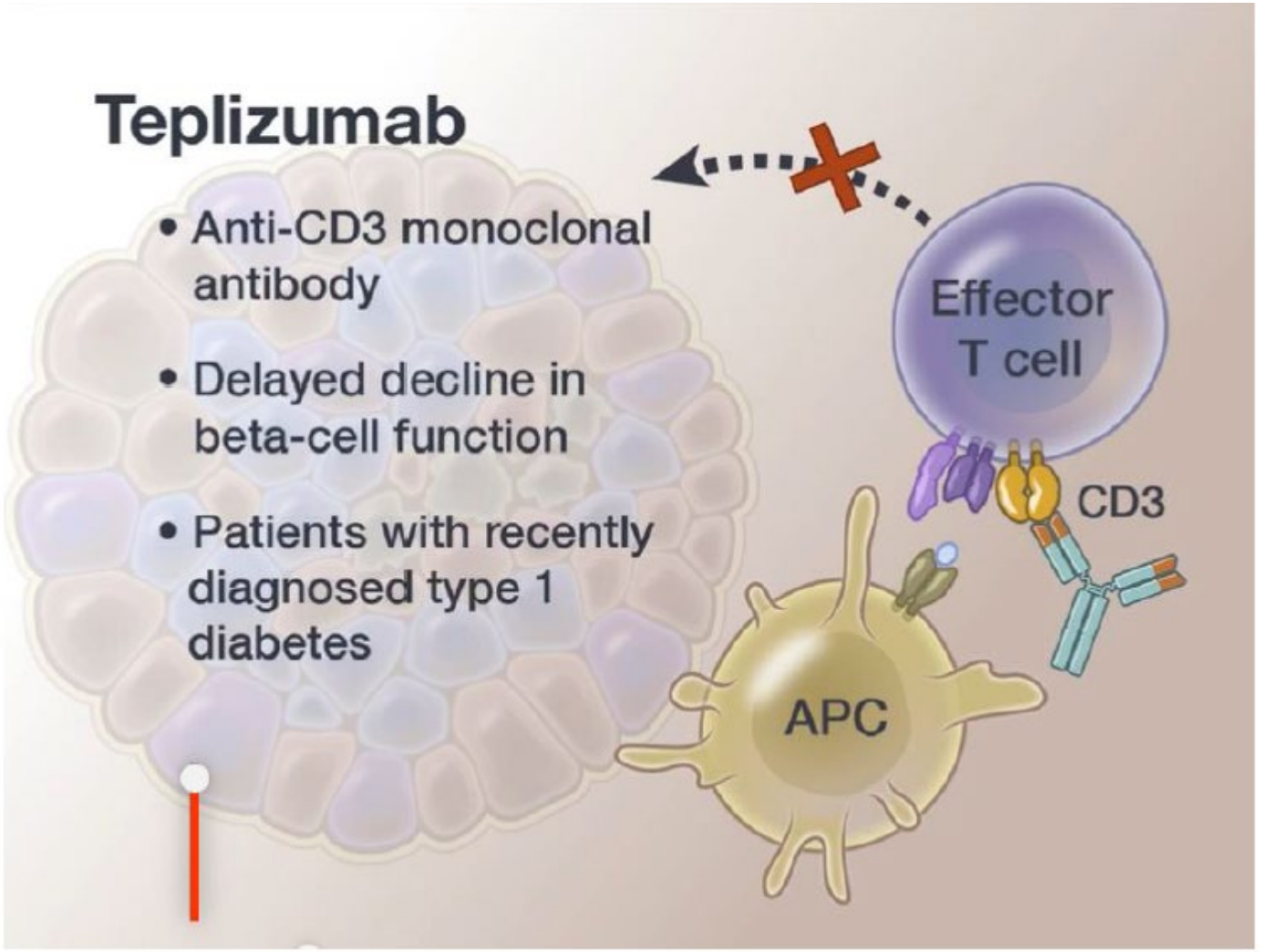
Teplizumab is a CD3-directed monoclonal antibody (mAb).

Binds to CD3 molecules on the surface of CD4+ and CD8+ T cells, with internalization of the teplizumab/CD3 complex from the surface of T cells.

Increases proportions of regulatory T cells and of exhausted CD8+ T cells in peripheral blood

Improves pancreatic ß cell function (based on C-peptide AUC levels), glucose tolerance, insulin secretory capacity

Higher levels of deactivated T lymphocytes are associated with slower progression of DMT1.



Herold KC, et al; Type 1 Diabetes TrialNet Study Group. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019 Aug 15;381(7):603-613

Teplizumab: Teplizumab Delayed Stage 3 Autoimmune T1D Diagnosis by Two Years

At Risk Study – fase II

Trial Fact Sheet

MOA

- Anti-CD3 mAb

EFFICACY

- **Primary endpoint** of delay in diagnosis of Stage 3 aT1D **was reached**
- **Teplizumab significantly delayed the clinical onset of autoimmune T1D** (Stage 3) **by 2 years versus placebo**[1]
- Stage 3 aT1D diagnosed in:
  - 19 (**43%**) teplizumab group
  - 23 (**72%**) placebo group
- Median time to Stage 3 aT1D diagnosis:
  - **48.4** months teplizumab group
  - **24.4** months placebo group
  - (HR: 0.41 [95% CI: 0.22, 0.78], p=0.006)

Kaplan-Meier curve with number of subjects at risk

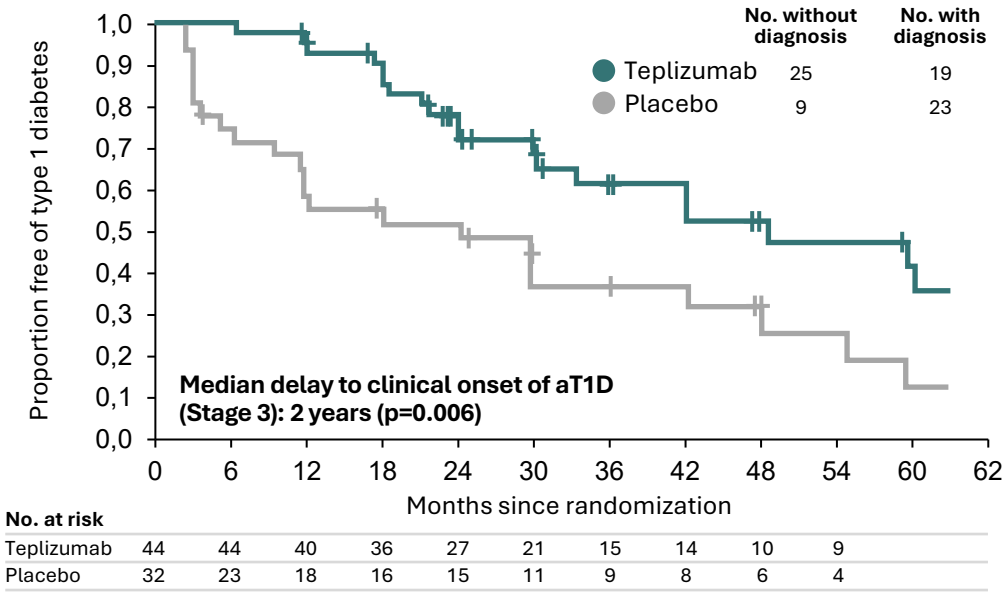


Figure adapted from Herold 2019.[1]

Participants were randomized to teplizumab daily for 14 days (n=44) or placebo (n=32).
Teplizumab was administered intravenously at a dose of 51 μg/m^2 on Day 0, 103 μg/m^2 on Day 1, 207 μg/m^2 on Day 2, 413 μg/m^2 on Day 3, and 826 μg/m^2 on Days 4 through 13.

Herold KC, et al. N Engl J Med. 2019;381(7):603-13.

Adverse Events

Among the adverse events that occurred in ≥5% of patients treated with teplizumab, the most common were **lymphopenia** (75%) and **itchy rash** (16%).

Adverse Event Category	Teplizumab		Placebo	
	Events (N=112)	Participants (N=44)	Events (N=23)	Participants (N=32)
	no.	*no. (%)*	*no.*	*no. (%)*
Blood or bone marrow†	45	33 (75)	2	2 (6)
Dermatologic or skin†	17	16 (36)	1	1 (3)
Pain	11	5 (11)	5	3 (9)
Infection	8	5 (11)	5	3 (9)
Gastrointestinal	5	4 (9)	3	3 (9)
Metabolic or laboratory	7	4 (9)	2	2 (6)
Pulmonary or upper respiratory	6	4 (9)	0	0
Constitutional symptoms	3	2 (5)	0	0
Allergy or immunologic	2	2 (5)	0	0
Cardiac, general	1	1 (2)	1	1 (3)
Endocrine	0	0	2	2 (6)
Vascular	1	1 (2)	1	1 (3)
Neurologic	1	1 (2)	0	0
Ocular or visual	1	1 (2)	0	0
Musculoskeletal or soft tissue	2	1 (2)	0	0
Hepatobiliary or pancreatic	0	0	1	1 (3)
Syndrome	1	1 (2)	0	0
Hemorrhage or bleeding	1	1 (2)	0	0

.

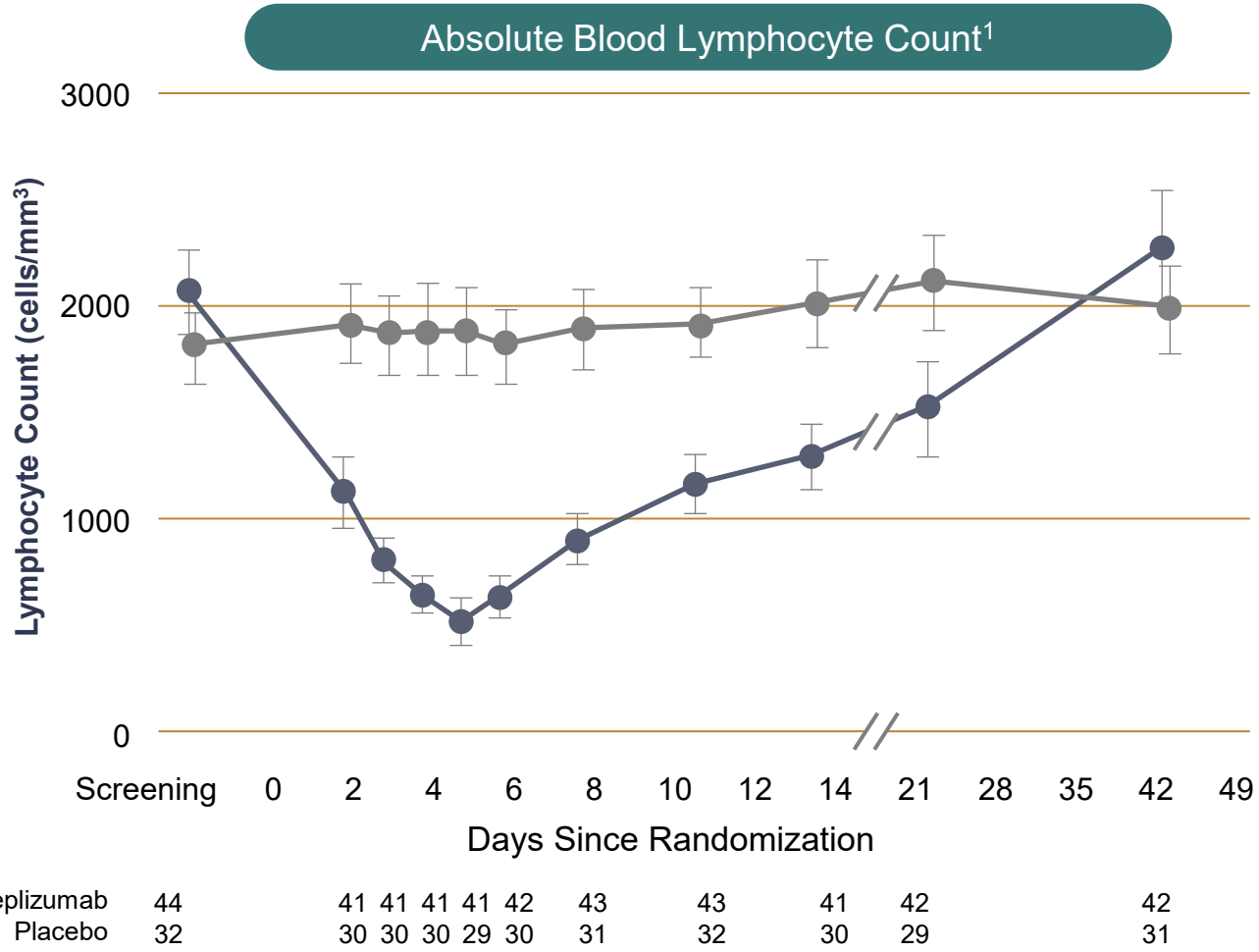
Herold KC, et al. N Engl J Med. 2019;381(7):603-13.

Teplizumab: The Decrease in Blood Lymphocyte Count with Teplizumab Was Transient[1]

Trial Fact Sheet

SAFETY

- **The decrease in lymphocyte count** may be driven by the mechanism of action of teplizumab on the immune system[1]
- Based on animal studies, T cells are believed to migrate to other compartments[2]
- **Lymphocytes began to recover on Day 6[1]**
- **Lymphocyte count returned to baseline levels** shortly after teplizumab treatment[1]



Error Bars – Means with 95% confidence intervals.

1. Herold KC, et al. N Engl J Med. 2019;381(7):603-13. 2. Waldron-Lynch F, et al. Sci Transl Med. 2012;4(118):118ra12.

Teplizumab: Phase 3 Study Demonstrated Significant Preservation of C-peptide Response at 78 Weeks vs Placebo (PROTECT)[1]*

PROTECT Study – fase III

Trial Fact Sheet

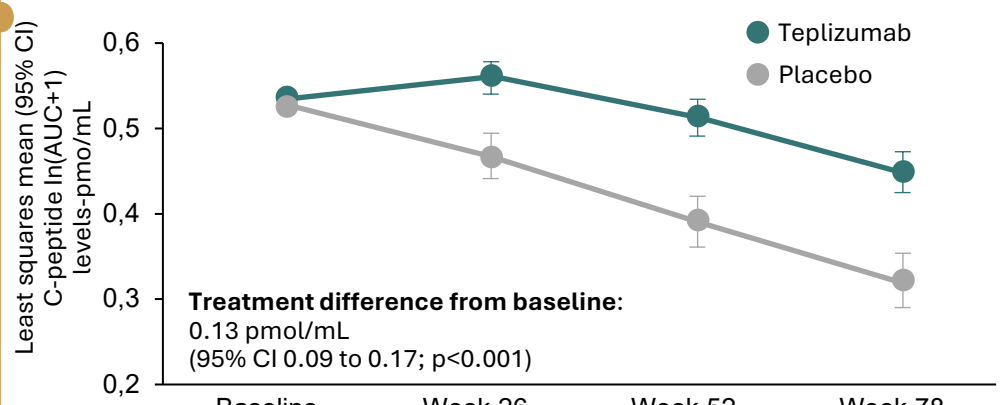
MOA
- Anti-CD3 mAb[2]

POSOLOGY
- Teplizumab: 9 mg/m² BSA per day, IV, in two 12-day courses 26 weeks apart0

TRIAL DESIGN
- Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of 328 children and adolescents with recent onset of Stage 3 autoimmune T1D[1]*

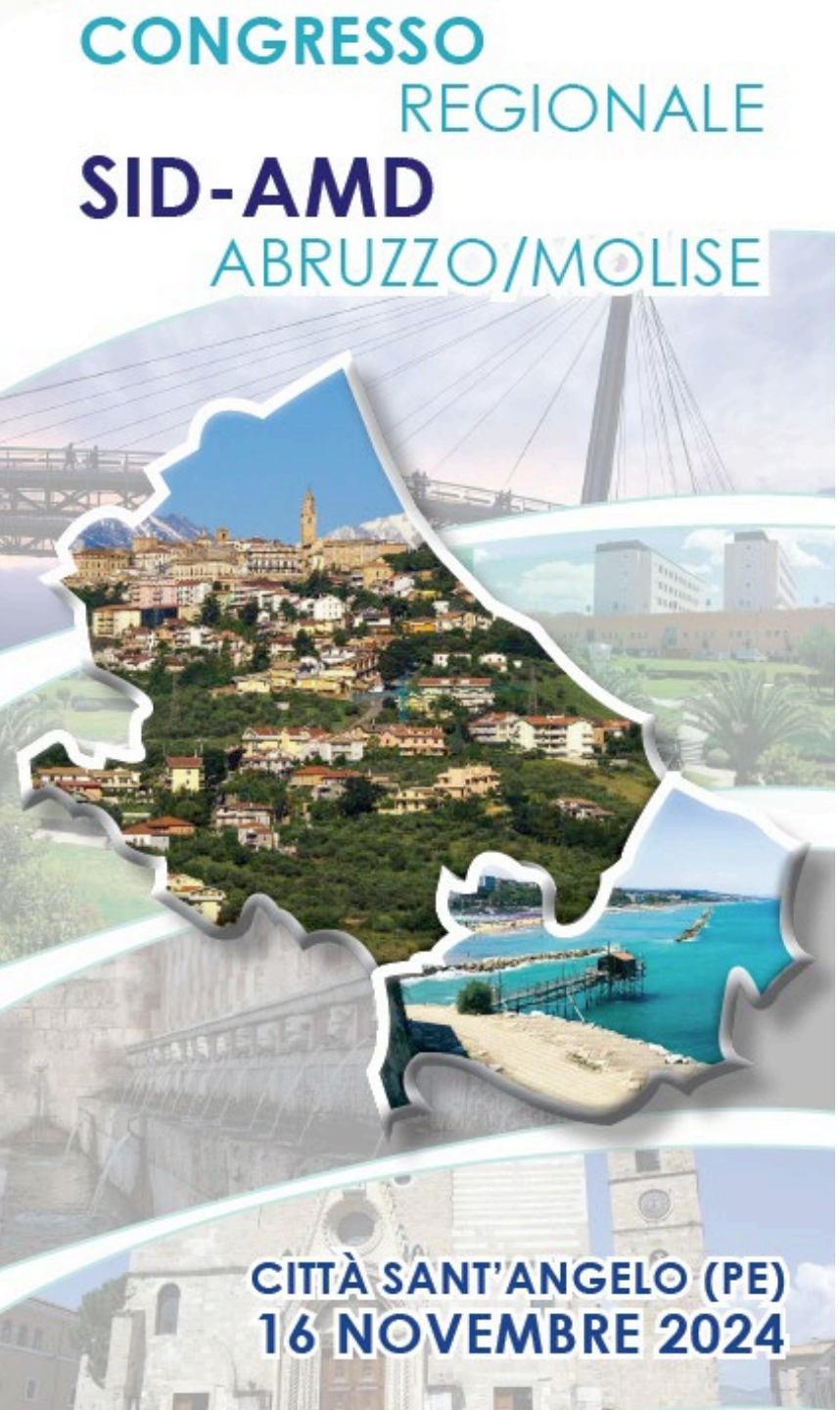
EFFICACY
- **The primary endpoint of change from baseline in beta-cell function, as measured by stimulated C-peptide levels at week 78, was reached[1]**
- There **were no differences between groups** in insulin doses required to meet glycemic goals, glycated hemoglobin levels, or time in target glucose range

SAFETY
- The most common adverse events were **headaches** (43.3%), nausea (42.4%), **rash** (39.6%), **decreased lymphocyte count** (33.6%), and **vomiting** (31.8%)†
- AEs leading to treatment discontinuation occurred in 15 (6.9%) and 3 (2.7%) of participants in the teplizumab and placebo groups, respectively[1‡]
- Covid-19 rates were comparable in the teplizumab (22.6%) and placebo (23.4%) groups



	Baseline	Week 26	Week 52	Week 78
Teplizumab	217	198	191	188
Placebo	111	101	98	88

1. Ramos EL, et al. N Engl J Med. 2023;389;23:2151-61. 2. Tzield (Teplizumab) Prescribing Information. December 2023. 3. Ramos EL, et al. N Engl J Med. 2023;389;23:2151-61. Supplementary material



Conclusions

- In Italy, a law has been approved that supports screening for type 1 diabetes (T1D) in the general population.

- The main objectives of the screening are:
  - Prevention of diabetic ketoacidosis (DKA) at the clinical onset of type 1 diabetes;
  - Identification of pre-symptomatic type 1 diabetes suitable for disease-modifying therapies.

- Teplizumab is the only drug currently approved to delay the onset of stage 3 disease in individuals over 8 years old in stage 2.

SID Società Italiana di Diabetologia 1964-2024

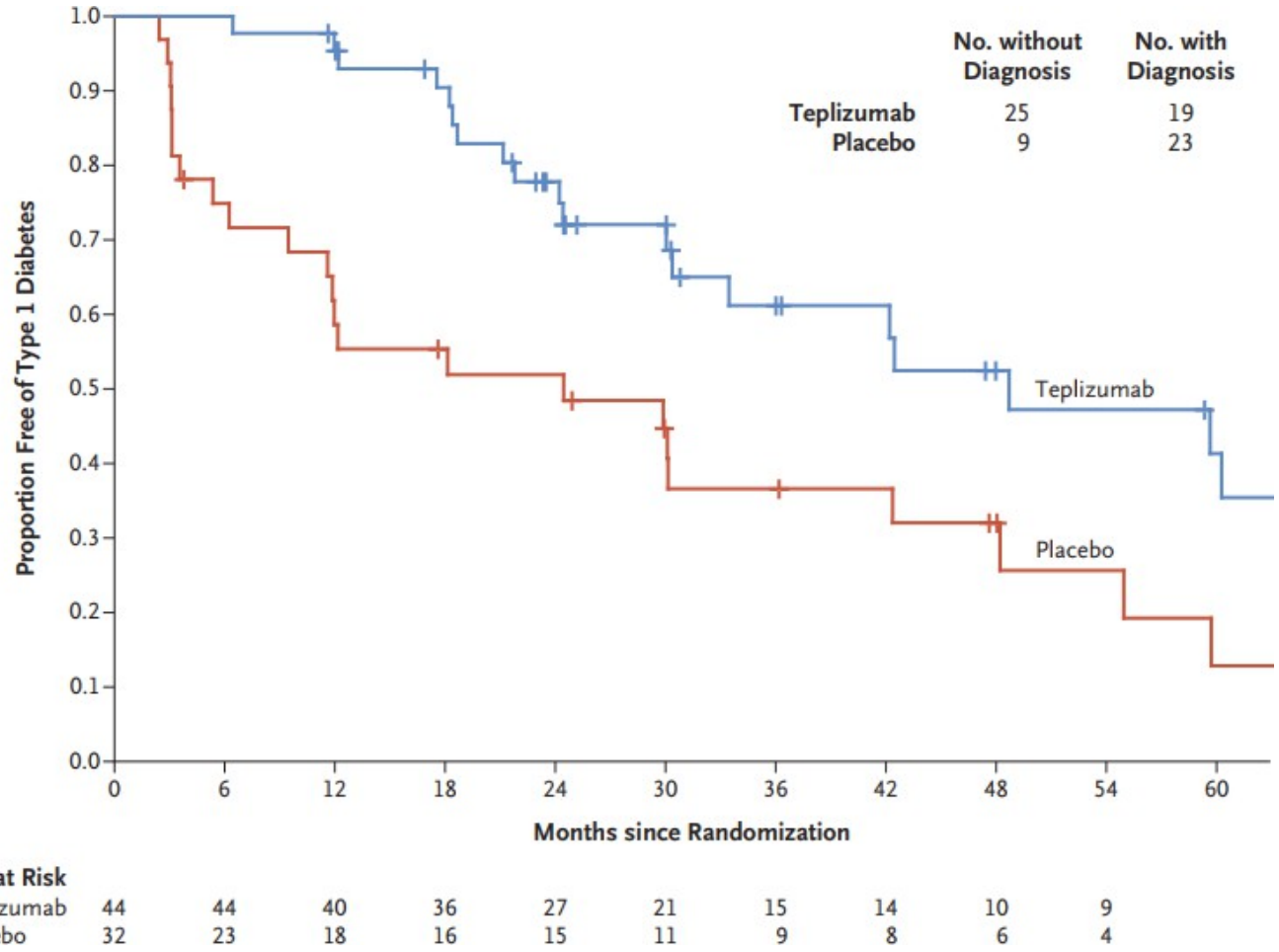
AMD 1974 Associazione Medici Diabetologi

Grazie!

AntiCD3 (Teplizumab) in family members of people with type 1 diabetes

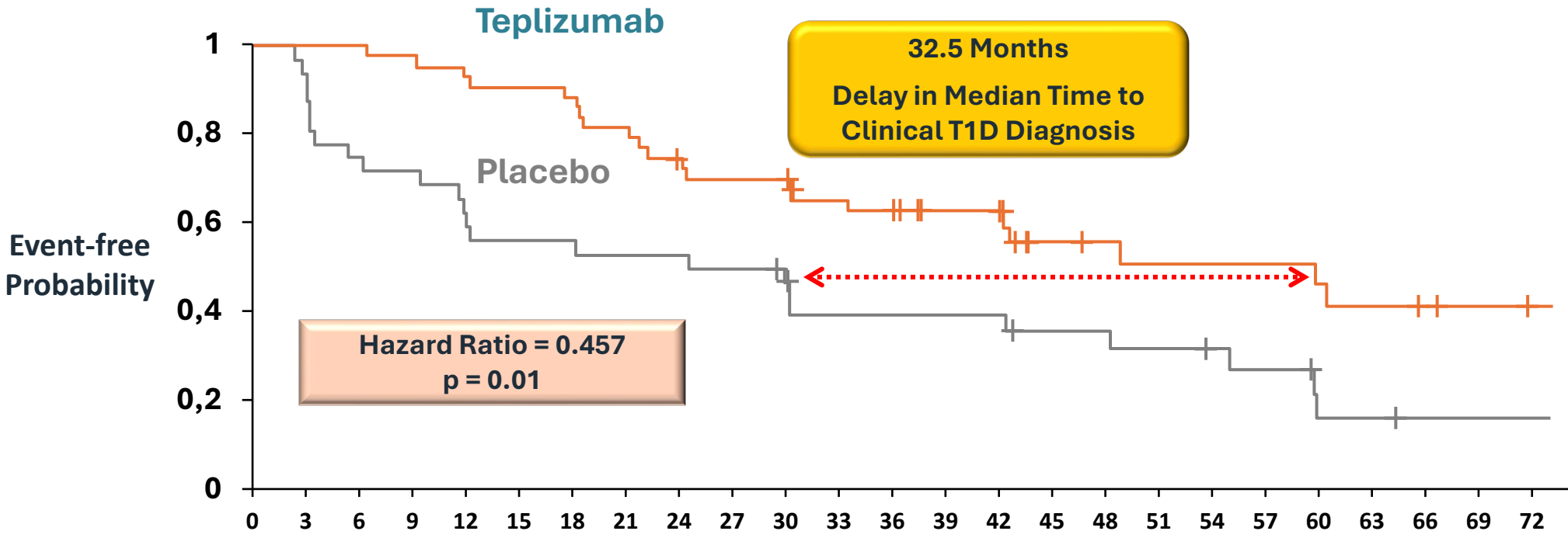
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)



Herold KC *et al.* N Engl J Med 2019.

Teplizumab Prevention Study
Sustained Delay over Extended Follow-Up



% With Onset	% Free of T1D	Median Time to Diagnosis
50%	50%	59.6 months
78%	22%	27.1 months

Number of Patients at Risk

Teplizumab	44	44	41	39	32	29	23	19	12	11	10	8	4
Placebo	32	24	19	18	17	14	11	11	9	7	3	2	2

Type 1 Diabetes TrialNet

Sims et al. Sci Trans Med 2021;13,eabc8980

Teplizumab: In a Follow-up Analysis, Teplizumab Delayed Onset of Autoimmune T1D by 2.7 Years versus Placebo[1]*

Trial Fact Sheet

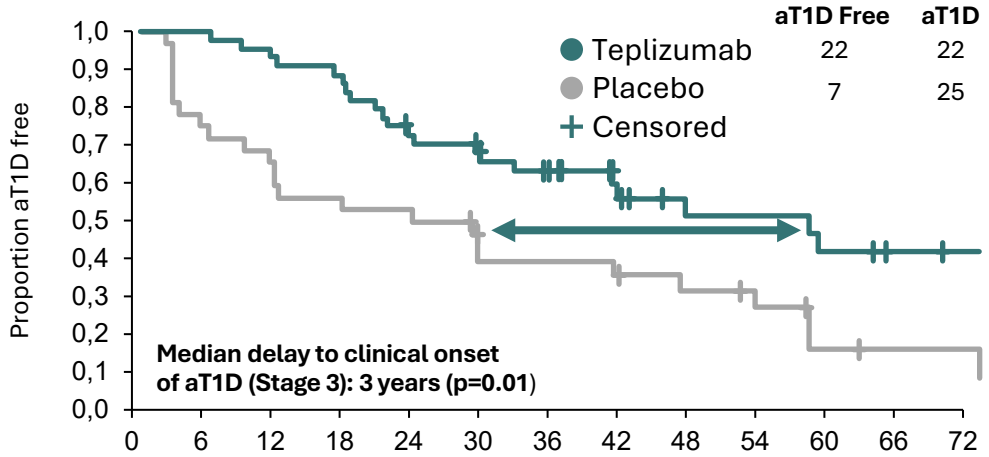
MOA

- Anti-CD3 mAb[1]

EFFICACY

- **Teplizumab delayed the clinical onset of autoimmune T1D** (Stage 3) **by 2.7 years versus placebo**[1]
- Median follow-up: **923 days**
- Stage 3 aT1D diagnosed in:[1]
  - 22 (50%) teplizumab group
  - 25 (78%) placebo group
- Median time to Stage 3 aT1D diagnosis:[1]
  - 59.6 months teplizumab group
  - 27.1 months placebo group
  - (HR: 0.457; p=0.01)
- Teplizumab treatment was associated with increased C-peptide AUC[1]

Kaplan-Meier curve with number of subjects at risk



No. at risk:													
Teplizumab	44	44	41	39	32	29	23	19	12	11	10	8	4
Placebo	32	24	19	18	17	14	11	11	9	7	3	2	2

8 people in the Teplizumab group **had not progressed to clinical aT1D** (Stage 3) **>5 years** after treatment[1†]

Figure adapted from Sims 2021.[1]

[†]10/13 subjects followed beyond 60 months were not diagnosed with aT1D: 8 were in the teplizumab group and 2 were in the placebo group.[1]

1. Sims EK, et al. Sci Transl Med. 2021;13(583):eabc8980.

Posologia

Teplizumab viene somministrato una volta al giorno per **14 giorni consecutivi** mediante **infusione endovenosa** della durata minima di 30 minuti.

La dose giornaliera è calcolata utilizzando un regime di dosaggio basato **sull'area di superficie corporea.**

La posologia prevede **65** µg/m2 il giorno 1; **125** µg/m2 il giorno 2; **250** µg/m2 il giorno 3; **500** µg/m2 il giorno 4; **1030** µg/m2 nei giorni 5-14.

Per almeno i primi 5 giorni di somministrazione, è necessaria una **premedicazione** prima dell'infusione di teplizumab con FANS, un antistaminico e/o un antiemetico.

Controindicazioni

Teplizumab **non è raccomandato**:

- Valori ematici significativamente anormali (riduzione della conta dei linfociti, piastrine o neutrofili, riduzione dell'emoglobina)
- ALT o AST elevate (> 2 volte il limite superiore della norma)
- Bilirubina elevata (> 1,5 volte il limite superiore della norma)
- Evidenza di infezione acuta da virus di Epstein-Barr o citomegalovirus, o altra infezione attiva grave o cronica
- Gravidanza

Criteria for population screening

Published 25/01/2024 - Edited 01/10/2024

The term screening is used in medicine to refer to diagnostic investigations performed in the population with the aim of identifying individuals with a disease or who are at risk of developing it. The World Health Organisation (WHO) has identified 10 criteria for a disease to be diagnosable through mass screening.

1. The pathological condition must be an important health problem.
2. There must be a therapy for the pathology sought.
3. Facilities for diagnosis and treatment must exist.
4. There must be a latent stage of the disease.
5. There must be a test or examination to ascertain the pathology in the latent phase.
6. The test must be well accepted by the population.
7. The natural history of the disease should be properly understood.
8. There must be agreement on treatment protocols and on whom to treat.
9. The total cost of discovering a case should be economically balanced in relation to overall medical expenditure.
10. The screening process should be prolonged over time.

The rationale behind T1D Screening

Arresting type 1 diabetes: several hopeful interventions

Immunomodulation

- **Teplizumab** (ani-CD3; Phase II)
- Rituximab (B cell depletion–anti-CD20; Phase II)
- Abatacept (CLTA-4 immunoglobulin; Phase II)
- **Anti-thymocyte globulin** (Phase IIb)
- Alefacept (anti-CD2; Phase II)
- **Baricitinib** (Phase II)
- GAD65 (Phase III)
- Anakinra (IL-1RA), canakinumab (anti-IL-1b)
- Mycophenolate mofetil + daclizumab (Phase II)
- DiaPep277 (Phase III; development halted)
- Rapa/IL-2 (Preclinical)
- Sitagliptin + lansoprazole (Phase II)
- Oral insulin (prevention)
- Nicotinamide (prevention)
- Thymoglobulin (Phase II)
- Tocilizumab (Phase II)

General anti-inflammatory agents

- Cyclosporine ±methotrexate
- Alpha-1 antitrypsin
- Imatinib (TKI)
- Verapamil (Phase III)

Specific anti-inflammatory agents

- Etanercept (anti-TNF; pilot)
- **Golimumab** (anti-TNF; Phase II)
- Anti-IL21 and liraglutide combined therapy (Phase II)

***No individual products are currently approved for use in clinical Stage 3 T1D. Teplizumab is approved for use in the USA only to delay the onset of Stage 3 T1D in adults and pediatric patients (8 years of age and older) with Stage 2 T1D (patient criteria defined in product labelling). Outside of the US, teplizumab is an investigational product and has not been authorized in the EU or any other country.** TKI, Tyrosine kinase inhibitor.

Allen LA and Dayan CM. Brit Med Bulletin 2021;140:76-90; Ludvigsson J, et al. NEJM 2012; 366: 433–2; Waibel M, et al. Trials 2022; 433; Cabrera SM, et al. Eur J Immunol 2016; 46: 1030-46; Gottlieb PA, et al. Diabetes Care 2010; 33: 826–32; Raz I, et al. Diabetes Care 2014; 37: 1392–1400; Baeyens A, et al. Diabetes 2013; 62: 3120–31; Griffin KJ, et al. Lancet Diabetes Endocrinol 2014; 2: 710–8; WC for T1D TrialNet Oral Insulin Study Group, et al. JAMA 2017; 318: 1891–02; Cabrera-Rode E, et al. Autoimmunity 2006; 39: 333–40; Gitelman SE, et al. Diabetologia 2016; 59: 1153–61; Greenbaum CJ, et al. JCI Insight 2021; 6: e150074; Forlenza GP, et al. JAMA 2023; 329:990-9; Teplizumab PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf (Last accessed February 2024).