Phase Ib clinical trial of IMCY-0098 in young adults with recent-onset type 1 diabetes

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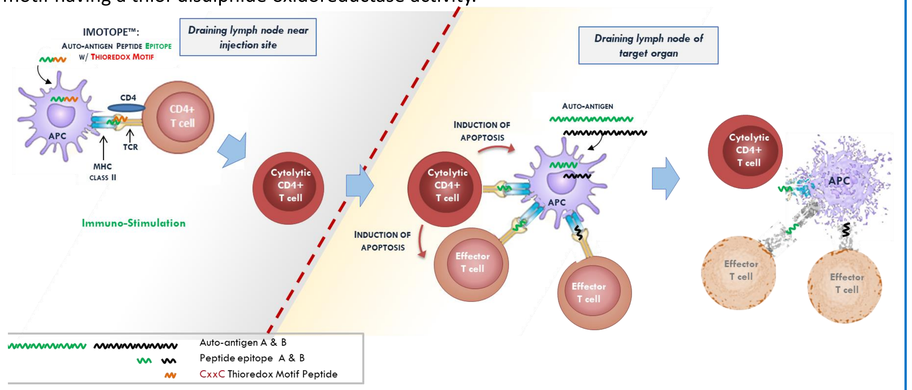
INTRODUCTION

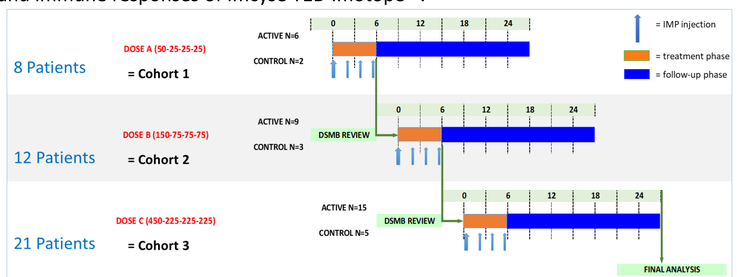
Imotopes™ are linear synthetic peptides comprising an MHC-II T-cell epitope sequence linked to a CXXC motif having a thiol-disulphide oxidoreductase activity.



Imotopes™ generate antigen-specific cytolytic memory CD4+ T cells which, by apoptosis, specifically eliminate antigen presenting cells (APCs) presenting the same T-cell epitope. They also eliminate pathogenic T cells activated by other epitopes on the same APC (bystander effect). Hence, Imotope™ technology has the potential to specifically eliminate pathogenic auto-immune responses and to cure Type 1 Diabetes (T1D). IMCY-0098™ is the Imotope developed for Type 1 diabetes (T1D).

STUDY DESIGN

In this dose escalation, placebo-controlled study, patients received 4 bi-weekly SC injections of one of the 3 tested doses or matching placebo. IMCY-0098 was injected with alum as adjuvant. Patients were followed-up for 6 months to evaluate the safety and immune responses of Imcyse T1D Imotope™.



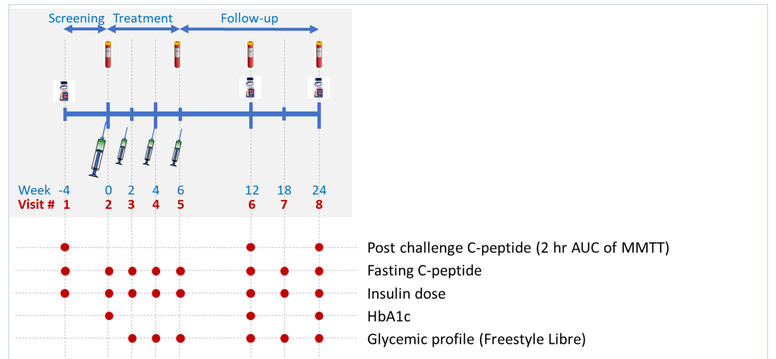
MAIN INCLUSION CRITERIA

Males and females **18 to 30 years** of age; BMI 17–28 kg/m2
Initial **diagnosis** of T1D according to ADA/WHO criteria within the past 6 months
Insulin requirement, as determined by the investigator
HLADR3-positive **and/or HLADR4**-positive
Presence of **at least one autoantibody** (GAD65, IA-2, or ZnT8)
Fasting **C-peptide at screening** >0.2 nmol/L and/or stimulated C-peptide ≥ 0.4 nmol/L

ENPOINTS

Primary objective: Assess, in adults with recent onset T1D, the safety of IMCY-0098 at three different doses and of placebo.
Secondary objective: Evaluate the clinical response to IMCY-0098 by assessing disease activity.
Exploratory objective: Evaluate and characterize the impact of IMCY-0098 on a panel of immune responses.

PATIENT JOURNEY



SAFETY

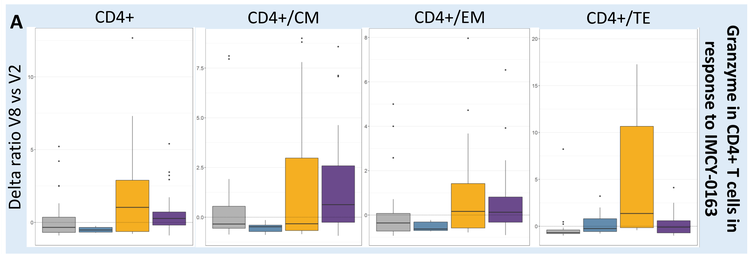
No safety issues were detected at any of the tested doses. Overall TEAE were of low intensity and short duration in all groups. No exacerbation of the disease was detected based on C-peptide levels monitoring. These results support the design of a phase II study including, if needed, a higher dose of IMCY-0098 and allow the inclusion of a younger population (< 18 years old).
In total, 3 serious TEAE have occurred during the study. Two of these events took place in the same patient in cohort 2 and were the results of a pre-existing condition that needed surgery during the study participation. These 2 serious TEAE were not related to the IMP. The third serious TEAE was a vestibular neuritis in a patient of cohort 3 that was reported at the last visit, more than 4 months after the last treatment injection. The event was reported as possibly related by the investigator but benign and of short duration. A SUSAR was reported accordingly.

Parameter		Placebo N = 10 n (%) E	IMCY-0098 Dose Level 50 µg + (3 x 25 µg) N = 6 n (%) E	150 µg + (3 x 75 µg) N = 9 n (%) E	450 µg + (3 x 225 µg) N = 16 n (%) E	Total N = 41 n (%) E
TEAEs		9 (90.0) 51	6 (100) 38	9 (100) 85	16 (100) 141	40 (97.6) 315
Solicited TEAEs		7 (70.0) 24	3 (50.0) 19	7 (77.8) 41	12 (75.0) 72	29 (70.7) 156
Unsolicited TEAEs		8 (80.0) 27	6 (100) 19	9 (100) 44	16 (100) 69	39 (95.1) 159
Serious TEAEs		0	0	1 (11.1) 2	1 (6.3) 1	2 (4.9) 3
Treatment-related TEAEs		6 (60.0) 25	4 (66.7) 18	7 (77.8) 42	11 (68.8) 65	28 (68.3) 150
TEAEs leading to study drug withdrawal		0	0	0	0	0
TEAEs leading to death		0	0	0	0	0
Overall grading	Grades					
	1	5 (50.0)	5 (83.3)	3 (33.3)	5 (31.3)	18 (43.9)
	2	3 (30.0)	1 (16.7)	6 (66.7)	10 (62.5)	20 (48.8)
	3	1 (10.0)	0	0	0	1 (2.4)
	4	0	0	0	1 (6.3)*	1 (2.4)

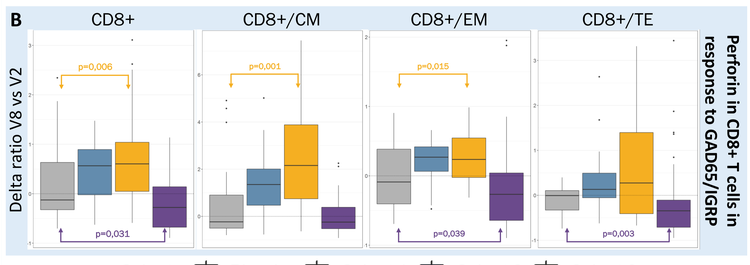
*adverse event recorded as grade 4 but site confirmed this TEAE was grade 1 (nausea).

IMMUNE RESPONSE

Detection of treatment specific CD4+ T cells producing GrB+ (cytolytic CD4+ cells)



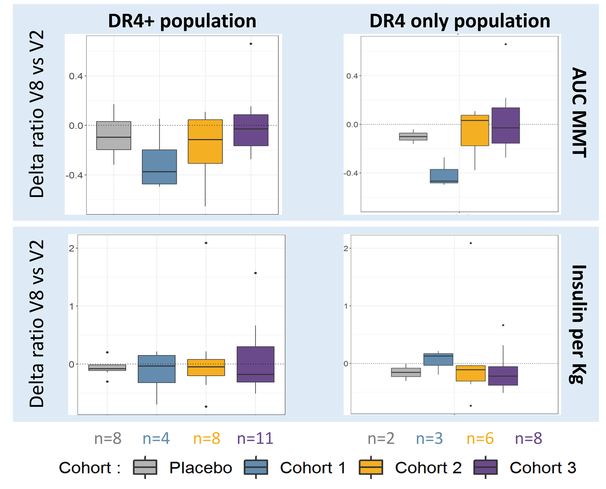
Decrease of disease-specific effector CD8+ T-cells at the highest dose of IMCY-0098



PBMCs were prepared from fresh blood and incubated with either IMCY-0163 (Wild Type epitope included in IMCY-0098, see panel A) or GAD65 and IGRP epitopes (panel B) for 12 days. Cells were analyzed by flow cytometry. Data are expressed as percentage of variation of the response ((V8-V2)/V2) of CD4+GrB+ (panel A) and CD8+Perforin+ (panel B). *Abbreviations: CM = Central Memory, EM = Effector Memory and TE = Terminal effector*

CLINICAL ANALYSIS

No significant differences for the clinical parameters were observed between cohorts due to small population and short duration of the study. Evolution of C-peptide (AUC MMTT) and daily total insulin doses are represented below. Patients expressing HLA-DR4 (DR4+ or DR4 only) and treated with intermediate or high dose showed a positive trend for these 2 endpoints and others (data not shown).



ASSOCIATION BETWEEN CLINICAL EVOLUTION AND IMMUNE RESPONSE

A link between evolution of clinical parameters and immune responses (detection of treatment-specific cytolytic CD4+GrB+ and reduction of disease-specific effector CD8+Perf+ cells) was identified for patients included in cohort 2 and 3. This was not the case for placebo and cohort 1 patients. This analysis (as well as others) was performed using Ariana Pharma's artificial intelligence-based KEM® technology (FDA-approved).

CONCLUSION: Results of the clinical trial have shown an excellent safety profile, reaching the primary study objective. Treated patients within all dose groups of IMCY-0098 showed no signs of disease exacerbation and no major treatment-related safety issues. In addition, promising early clinical trends were observed including reduced decrease of fasted C-peptide level. Finally, cytolytic CD4 T-cells were detected for the first time in humans, along with a concomitant decrease of effector T cells involved in the disease mechanism of T1D. Further analyses showed link between positive trends on clinical endpoints and immune findings. These preliminary results will need to be confirmed in a larger Phase II study.