Hyleukin-7, a long-acting interleukin-7, increased absolute lymphocyte counts after subcutaneous and intramuscular administration in healthy subjects

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Abstract

Higher lymphocyte counts predict lower mortality in patients with various oncologic malignancies. Interleukin-7 (IL-7), a homeostatic cytokine, plays a critical and non-redundant role in developing T-cells and maintaining immune functions after development. IL-7 is a potent T-cell amplifier, thereby contributing to immune reconstitution, which may result in clinical benefits. A randomized, double-blind, placebo-controlled, dose-escalation, phase I study was conducted to assess the safety, tolerability, pharmacokinetic and biological properties of Hyleukin-7 (human IL-7 fused to hyFc^{TM}) administered subcutaneously (SC) and intramuscularly (IM) to healthy volunteers.

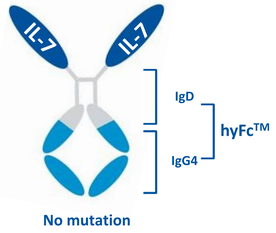
Ten subjects randomly received Hyleukin-7 or its matching placebo in an 8:2 ratio in each of three cohorts at 20 and 60 μg/kg SC and 60 μg/kg IM. Dose escalation was determined on 28 days after study drug administration based on the safety and tolerability data. Subjects were followed up to 56 days after dose.

Hyleukin-7 was well tolerated with single SC and IM administration and no serious adverse event reported as well as cytokine release syndrome. Injection site reactions were the most common treatment-emergent adverse events, which resolved spontaneously without treatment. Hyleukin-7 was slowly but steadily absorbed and its terminal half-life ranged 48-112 hours. Furthermore, Hyleukin-7 increased absolute lymphocyte counts (ALC) in a dose-dependent manner which lasted during the observed period of 56 days after dose. The mean maximum increase in ALC from baseline was seen 3 weeks after dose. IM Hyleukin-7 increased ALC greater exposure than SC Hyleukin-7 did at the same dose (111.4% IM vs. 75.1% SC). In all of the doses, Hyleukin-7 markedly increased the numbers of all peripheral CD4+ and CD8+ lymphocyte subsets (i.e., naïve, EM, CM and TEMRA). These increases are attributed to increased cell proliferation as evidenced by enhanced expression of Ki-67.

Hyleukin-7^{TM} (rhIL-7-hyFc)

Human Ig Isotypes	IgG1	IgG4	IgD
Hinge flexibility	++	+	++++
ADCC	++++	++	-
CDC	++	-	-
Binding of FcRn	++++	++++	-
Half life (days)	21	21	3

Immunology Fifth Edition, by Kuby etc. p 90
J of Immunol. 1997 159: 3372
J of Immunol. 2004 172: 2925



Broad applicability

Retained bioactivity
(flexible hinge, less steric hindrance)

No Cytotoxicity
(ADCC or CDC)

Long-acting
(FcRn-mediated recycling)

Structure of Hyleukin-7^{TM}

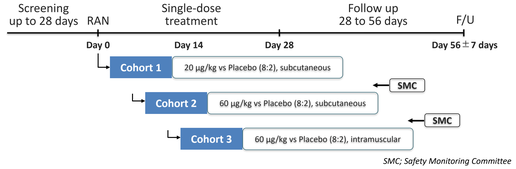
- **Hyleukin-7^{TM}** is a long-acting recombinant human interleukin-7 fused to hybrid Fc (hyFc^{TM}) with IgD and IgG4.
- A novel Fc-based platform technology, hyFc^{TM} extends half-life and increases of bioactivity of fused proteins.

Objectives

To assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of Hyleukin-7 in healthy volunteers

Study Design

A Phase I, randomized, double-blind, placebo-controlled, single ascending dose study (ClinicalTrials.gov Identifier: NCT02860715)



SMC; Safety Monitoring Committee

RESULTS

Table 1. Demographic and Other Characteristics (n=30, all randomized subjects)

	Placebo (n=6)	Hyleukin-7 20 μg/kg, SC (n=8)	Hyleukin-7 60 μg/kg, SC (n=8)	Hyleukin-7 60 μg/kg, IM (n=8)	Total (n=30)
Baseline Age (years), mean (SD)	30.00 (5.40)	28.63 (6.16)	25.88 (7.41)	24.50 (3.85)	27.07 (5.98)
Gender (Male), n (%)	5 (83.33)	5 (62.50)	4 (50.00)	6 (75.00)	20 (66.67)
BMI, mean (SD)	22.87 (2.19)	21.59 (2.69)	23.31 (2.97)	22.09 (1.73)	22.44 (2.43)
Smoking History, n (%) Non-smoker	4 (66.67)	7 (87.50)	8 (100.00)	7 (87.50)	26 (86.67)
Drinking History, n (%) Non-drinker	1 (16.67)	5 (62.50)	7 (87.50)	2 (25.00)	15 (50.00)

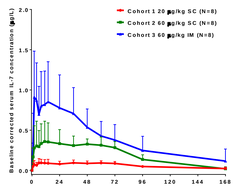
*BMI, Body Mass Index; SD, standard deviation

Pharmacokinetics (PK) and Pharmacodynamics (PD)

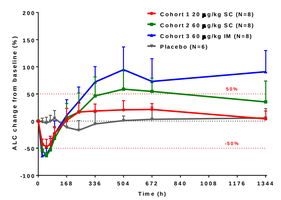
- A single dose of 20, 60 μg/kg SC, 60 μg/kg IM Hyleukin-7 or placebo was administered
- Dose dependent PK/PD profiles were observed

Figure 2. PK and PD of Hyleukin-7 in healthy volunteers (A) Serum Hyelukin-7 Concentration-Time profiles (linear scale) following single subcutaneous or intravenously administration. Mean change from baseline in (B) absolute lymphocyte counts (linear) and (C) subset analysis for Hyleukin-7 and placebo dosing groups. CFB; change from baseline.

(A) Pharmacokinetics (linear)



(B) Pharmacodynamics (change from baseline)



(C) Pharmacodynamics (subset analysis)

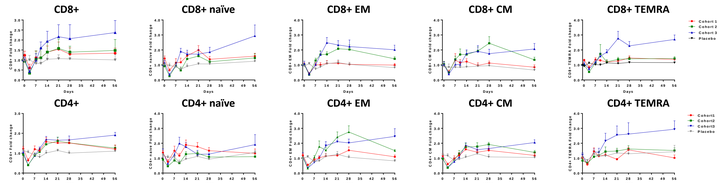


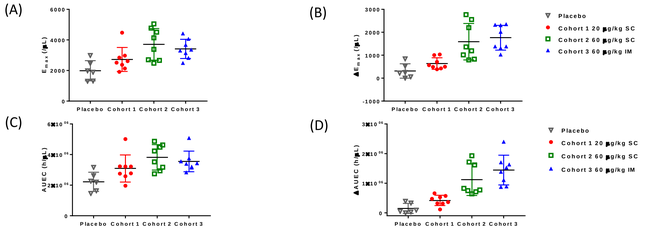
Table 2. Baseline corrected† Pharmacokinetic parameters after a single subcutaneous or intramuscular administration of Hyleukin-7

Pharmacokinetic parameters	20 μg/kg SC (N=8)	60 μg/kg SC (N=8)	60 μg/kg IM (N=8)
T_{max} (h)	42.00 (6.00 - 72.02)	36.00 (4.00 - 72.03)	4.00 (2.00 - 35.78)
C_{max} (μg/L)	0.12 ± 0.04	0.47 ± 0.25	1.16 ± 0.51
AUC_{last} (h·μg/L)	10.17 ± 1.95	30.98 ± 8.36	64.85 ± 25.06
AUC_{inf} (h·μg/L)	12.35 ± 2.78	33.30 ± 8.84	83.42 ± 57.94
$t_{1/2}$ (h)	52.70 ± 32.08	26.83 ± 15.60	63.26 ± 49.41
CL/F (L/h)	101.26 ± 25.15	128.41 ± 31.42	55.47 ± 20.81
V_d/F (L)	7243.30 ± 3500.67	5097.81 ± 3707.54	4577.87 ± 3666.35

*All data are presented as mean ± standard deviation and T_{max} values are presented as median (minimum – maximum)
†Baseline corrected; the mean concentrations obtained prior to study drug administration (i.e. screening, Day-1, and pre-dose) was subtracted from all of the concentrations post-dose. For any negative value of concentration, 0 was used instead.

RESULTS

Figure 3. Individual (A) Emax, (B) ΔE_{max}, (C) AUEC and (D) ΔAUEC of Hyleukin-7 after a single subcutaneous (SC) or intramuscular (IM) administration of GX-I7 (or placebo)



Safety Results

- All treatment-emergent adverse drug reactions were mild to moderate and mostly transient.
- No treatment-related serious adverse events reported.

TEAE n(%),[case]	Placebo (N=6)	Hyleukin-7 20 μg/kg SC (N=8)	Hyleukin-7 60 μg/kg SC (N=8)	Hyleukin-7 60 μg/kg IM (N=8)	Total (N=30)
Number of Subjects with TEAEs	2(33.33) [10]	8(100.00) [11]	8(100.00) [23]	8(100.00) [14]	26(86.67) [58]
Number of Subjects with ADRs	2(33.33) [10]	8(100.00) [11]	8(100.00) [23]	8(100.00) [14]	26(86.67) [58]
Severity[1)]					
Mild	10	11	14	13	48
Moderate	0	0	9	1	10
Severe	0	0	0	0	0
Number of Subjects with Serious TEAEs	0	0	0	0	0
Most frequently reported TEAEs					
Injection site reaction	1(16.67)[1]	8(100.00)[8]	8(100.00)[8]	8(100.00)[8]	25(83.33)[25]
Headache	2(33.33)[3]	1(12.50)[1]	1(12.50)[1]	0(0.00)[0]	4(13.33)[5]
Lymphadenopathy	0(0.00),[0]	0(0.00)[0]	2(25.00)[2]	0(0.00)[0]	2(6.67)[2]
Pyrexia	1(16.67)[1]	0(0.00)[0]	0(0.00),[0]	1(12.50)[1]	2(6.67)[2]
Dizziness	0(0.00),[0]	0(0.00)[0]	1(12.50)[1]	1(12.50)[1]	2(6.67)[2]
Oropharyngeal pain	1(16.67)[1]	0(0.00)[0]	1(12.50)[1]	0(0.00)[0]	2(6.67)[2]
Productive cough	1(33.33)[2]	0(0.00)[0]	1(12.50)[1]	0(0.00)[0]	2(6.67)[3]

1) Severity is displayed as number of events

CONCLUSIONS

- Overall, single subcutaneous and intramuscular administrations of Hyleukin-7 at the dose range of 20 to 60 μg/kg appear to be safe and well-tolerated in healthy volunteers.
- Hyleukin-7 was slowly absorbed, particularly after subcutaneous administration (T_{max}: 36-40 hours post-dose), and was slowly removed from the body ($t_{1/2}$: 48-112 hours), resulting in a flat PK profile, typically seen in biologics.
- Intramuscular Hyleukin-7 was more rapidly absorbed than subcutaneous Hyleukin-7, and also showed greater exposure at the same dose of 60 μg/kg, although the difference was not statistically significant.
- The ALC increased in a dose-dependent manner after Hyleukin-7 subcutaneous administration. Intramuscular administration of Hyleukin-7 showed higher increase (111.4% vs. 75.1% for percent change from baseline at the same dose) in ALC compared to subcutaneous administration at the same dose of 60 μg/kg.
- The increase in ALC peaked around 3 weeks after administration of Hyleukin-7, and it lasted over several weeks since the administration.

Additional information on other Hyleukin-7 oncology clinical trials

- In advanced or metastatic solid cancer study with Hyleukin-7, dose-dependent increase in absolute lymphocyte counts (ALCs) were observed.
- Repeated intramuscular administration of Hyleukin-7 was well-tolerated in the dose range studied.

[ClinicalTrials.gov Identifier: NCT03478995]

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