NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

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UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
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Efficacy and SARS CoV-2 viral decay in nasopharynx, saliva and plasma in high-risk patients treated with monoclonal antibodies (mAb).

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DiSS

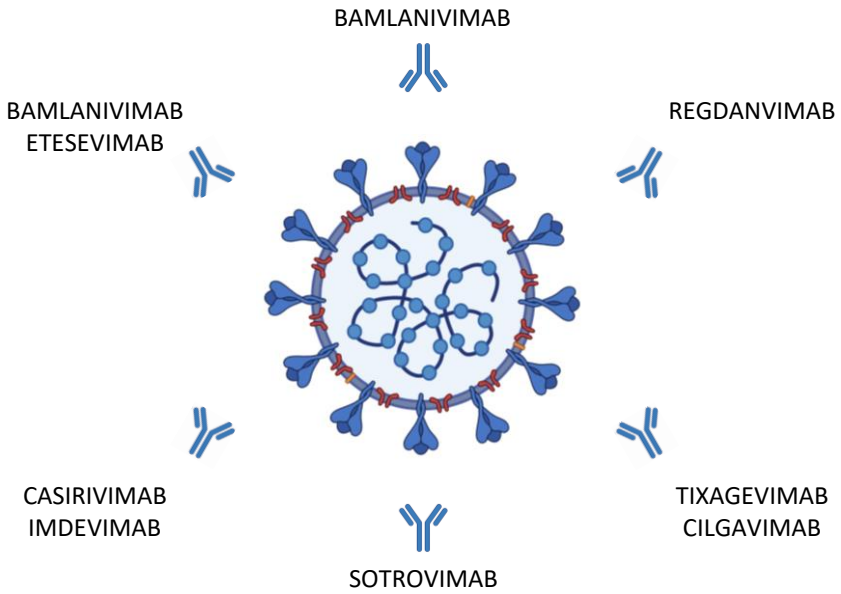
Conflict of interest

- No conflict of interest to declare

Background

- SARS-CoV-2 Monoclonal antibodies (mAbs) **target the SARS-CoV-2 spike protein**, which the virus utilizes to enter host cells, thus **blocking viral attachment and entry into human cells.**

- **RCT have shown that mAbs were associated with clinical benefits** in treating COVID-19 caused by variants predominant during the earlier stages of the pandemic.



Corti D. et al, Cell. 2021 Jun 10;184(12):3086-3108.

Background

- Real-life data demonstrated that **Casirivimab/Imdevimab and Sotrovimab were similarly associated** with a reduced risk of hospitalization or death in mild-moderate patients with **Delta** variant.

- Conversely, real-world evidence about **Sotrovimab during the Omicron was contrasting**: this mAb resulted effective in preventing clinical progression in some observational studies, while it did not reduce mortality in others.

- Furthermore, **Sotrovimab could have a partial reduction in neutralisation activity in vitro against Omicron subvariants**, even if these data are difficult to interpret; it could maintain preserved effector functions such as antibody-dependent cell cytotoxicity and antibody-dependent cell phagocytosis.

Huang DT, JAMA Network Open 2022;5(7):e2220957; Gupta et al, N Eng J of Med, 2021; 385(21):1941-1950; Gupta et al, JAMA. 2022;327(13):1236–1246; Piccicacco et al, J Antimicrob Chemother. 2022 Sep 30;77(10):2693-2700; Amani B, Rev Med Virol 2022; 32(6):e2402.

Background

- Given the not well-known efficacy against the circulating viral variants, **mAbs are currently recommended** in patients diagnosed with a mild-moderate infection at **high risk of clinical progression and contraindications to antivirals**.

- Given the well-established efficacy of COVID-19 vaccination in protecting from severe disease, **the additional clinical and virological value of mAbs in high risk vaccinated people needs further investigation**.

Iketani S et al, Nature 2022; 604(7906):553-556; Hoffmann M et al, Cell 2022;185(3):447-456; Bruel T et al, Cell Rep Med 2022; 3(12):100850
https://www.covid19treatmentguidelines.nih.gov; Yang ZR et al, Lancet Microbe, 2023; 4(4):e236-e246..

Aim of the study

- To investigate the **efficacy** of mAbs (Bamlanivimab, Bamlanivimab/Etesevimab, Casirivimab/Imdevimab, Sotrovimab) in a cohort of patients diagnosed with a mild-moderate SARS CoV-2 infection, at high risk of clinical progression

- To study **SARS CoV-2 viral load** in three different compartments (nasopharynx (NP), saliva and plasma) according to vaccination.

ENDPOINTS	
PRIMARY	**Comparison of efficacy** (composite outcome defined as proportion of patients with clinical recovery vs hospitalization after treatment vs death) between unvaccinated (unvax) and vaccinated patients (vax);
SECONDARY	**Virological clearance at day 7 after treatment** (T1, antigenic or molecular NP swab) and median time from symptoms' onset to first antigenic or molecular negative NP swab according to vaccination
	Comparison of NP, saliva and plasma viral load between unvaccinated (unvax) and vaccinated patients (vax).

Study and Methods

HR* Outpatients

+

SARS-CoV-2 infection

+

mAbs°

+

03/2021 → 05/2022

Time			
T0 (Day of treatment)	**X**	**X**	**X**
T1 (7 days after treatment)	**X**	**X**	**X**
T2 (14 days after treatment)	**X**	**X**	**X**

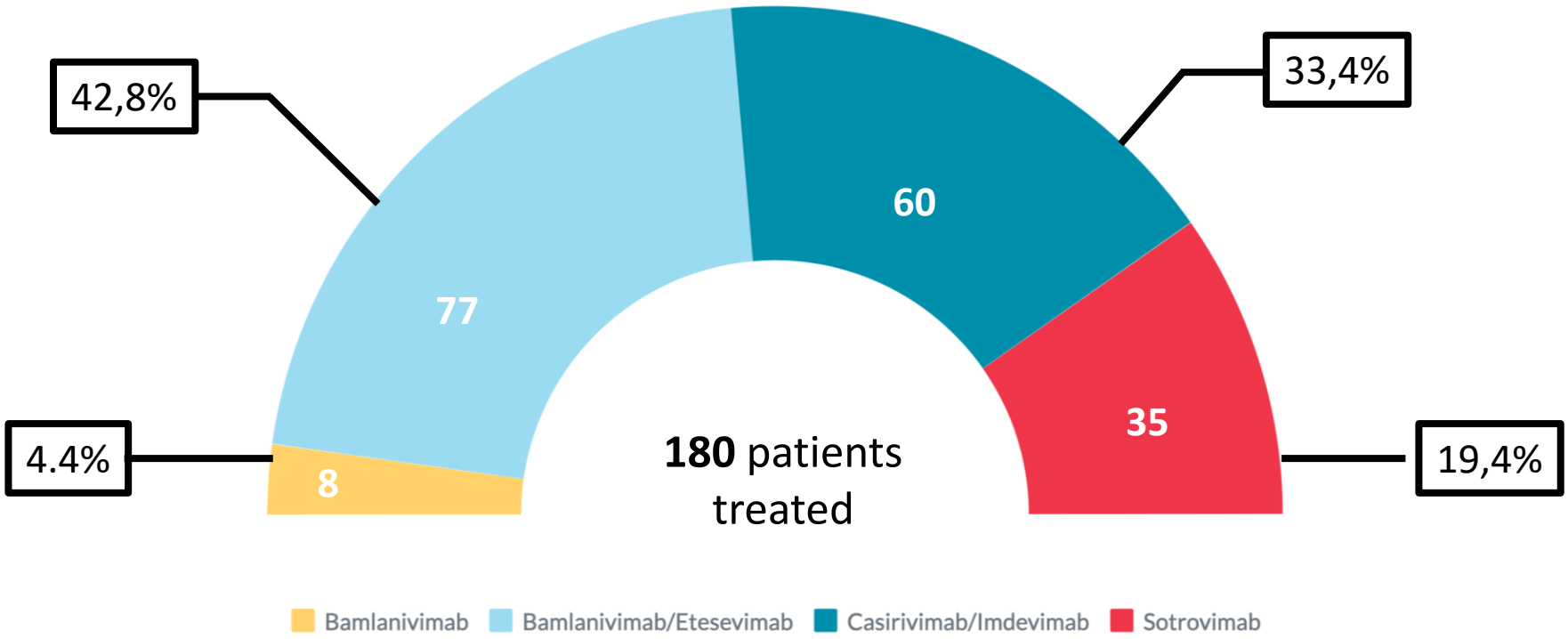
- SARS CoV-2 viral load was measured on NP, saliva and plasma by quantitative RT-PCR (SARS CoV-2 RNA was extracted by the QiAmp RNA viral kit and viral load was measured on specimens by quantitative RT-PCR targeting the viral N gene).
- In a subgroup of patients viral variant was available (Sanger sequencing of the S gene was performed for variants characterization).

STATISTICAL ANALYSIS: Mann-Whitney, Chi-square, Wilcoxon test and univariable/multivariable logistic regression were used for statistics.

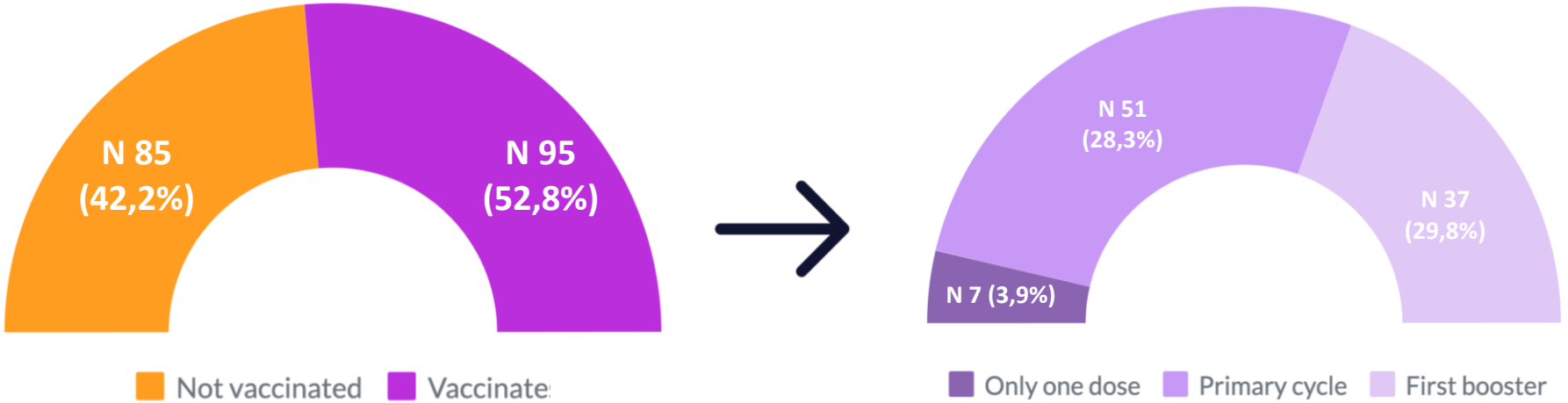
* Risk factors for progression were: age >65 years, chronic diseases or immunodeficiencies.

° Patients were treated ≤ 10 days from symptoms onset.

Results: Ambulatory setting treatments



Results: Vaccination status in ambulatory patients



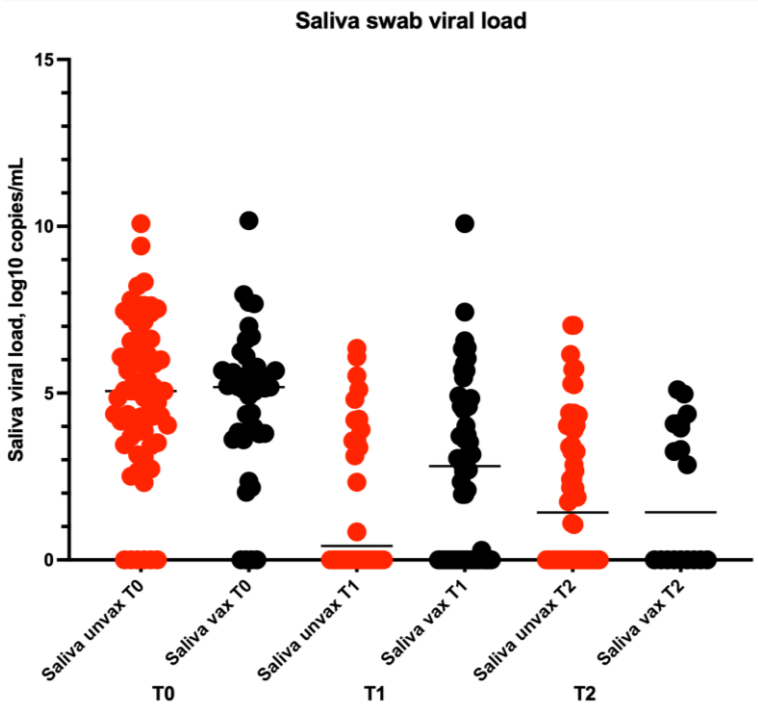
Results: Demographic and clinical characteristics of patients with mild/moderate COVID-19, according to vaccination

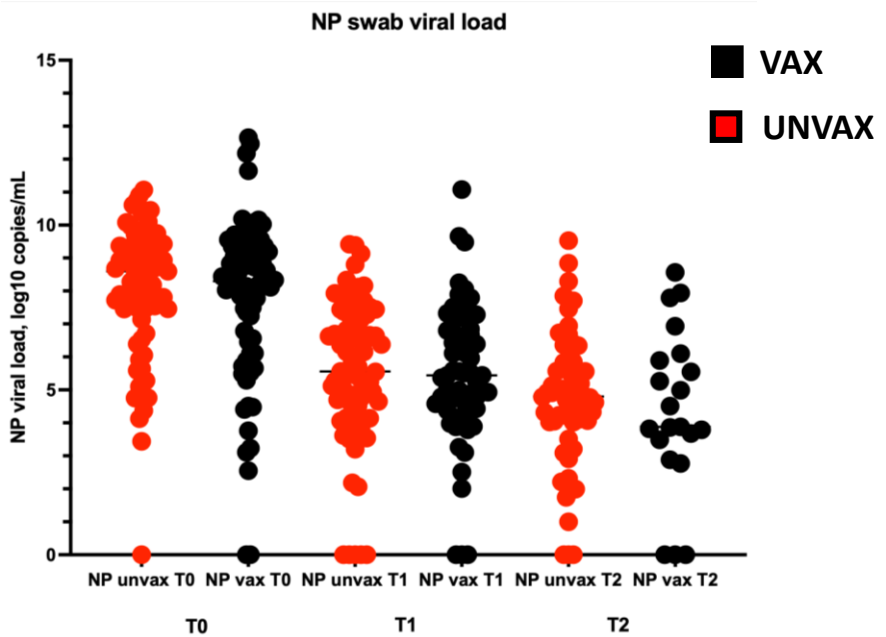
Characteristics	Study population N 180	Unvaccinated patients N 85 (42.2%)	Vaccinated patients N 95 (52.8 %)	p values
Age [years], median (IQR)	65 (50-74)	59 (48-72)	67 (55-77)	0.010
Female sex, n (%)	77 (42.8%)	37 (43.5%)	40 (42.1%)	0.847
Risk factor, n (%): Chronic diseases Immunodeficiency/Cancer BMI > 30 Only age > 65 years Unknown	 99 (55%) 34 (18.9%) 25 (13.9%) 18 (10%) 4 (2.2%)	 45 (52.9%) 14 (16.6%) 19 (22.4%) 6 (7%) 1 (1.1%)	 54 (56.8%) 20 (21%) 6 (6.3%) 12 (12.6%) 3 (3.2%)	0.016
Viral variant, n (%): Alfa Beta C.36.6 Delta Omicron L18F	N 103 49 (27.2%) 1 (0.6%) 2 (1.1%) 37 (20.6%) 13 (7.2%) 1 (0.6%)	N 69 47 (68.1%) 1 (1.4%) 2 (2.9%) 13 (18.8%) 5 (7.2%) 1 (1.4%)	N 34 2 (5.9%) 0 0 24 (70.6%) 8 (23.5%) 0	<0.001
Days from symptom onset to antiviral treatment, median (IQR)	4 (2-6)	4 (3-7)	3 (2-5)	0.005

Results: Clinical efficacy and virological clearance according to vaccination

Characteristics	Study population N 180	Unvaccinated patients N 85 (42.2%)	Vaccinated patients N 95 (52.8%)	p values
Outcome, n (%): Recovery Hospitalization Death Lost to follow up	 156 (86.7%) 19 (10.6%) 0 5 (2.8%)	 62 (72.9%) 18 (21.2%) 0 5 (5.9%)	 94 (98.9%) 1 (1.1%) 0 0	<0.001
Adverse events, n (%):	20 (11.1%)	17 (20%)	3 (3.2%)	<0.001
Virological clearance at T7, n (%): No Yes Unknown	 115 (63.9%) 64 (35.6%) 1 (0.5%)	 58 (68.2%) 26 (30.6%) 1 (1.2%)	 57 (60%) 38 (40%) 0	0.557
Days from symptom onset to virological clearance, median (IQR)	16 (12-21)	18 (13-22)	15 (11-19)	0.012

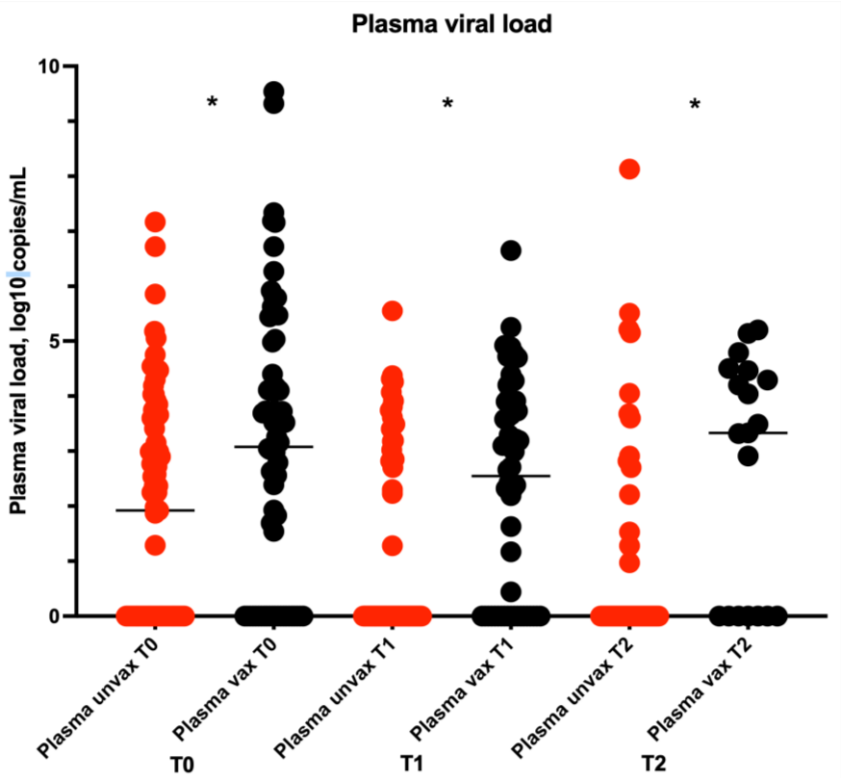
Results: Viral load on saliva and NP at the different time points according to vaccination





- Median NP and saliva viral load were similar at T0 between vaccinated and unvaccinated patients and presented a similar decay at T1-T2

Results: Viral load on plasma at the different time points according to vaccination



VAX

UNVAX

Legend: * $p<0.05$ for comparison between unvax and vax.

- Vaccinated patients displayed higher median plasma viremia at T0, compared to unvaccinated individuals, that was maintained at T1-T2.

Results: Proportion of patients with positive SARS CoV-2 NP, saliva and plasma viral load in unvaccinated and vaccinated patients

SARS CoV-2 positive viral load	Unvaccinated patients	Vaccinated patients	p values
NP swab, T0: Positive viral load	N 75 74 (98.7%)	N 74 72 (97.3%)	0.552
Saliva swab, T0: positive viral load	N 65 59 (90.8%)	N 41 37 (90.2%)	0.928
Plasma viral load, T0: positive viral load	N 75 40 (53.3%)	N 70 48 (68.6%)	0.060
NP swab, T1: positive viral load	N 73 68 (93.2%)	N 61 58 (95.1%)	0.638
Saliva swab, T1: positive viral load	N 60 38 (63.3%)	N 28 14 (50%)	0.236
Plasma, T1: positive viral load	N 72 22 (30.6%)	N 57 37 (64.9%)	<0.001
NP swab, T2: positive viral load	N 59 56 (94.9%)	N 21 18 (85.7%)	0.169
Saliva swab, T2: positive viral load	N 54 29 (53.7%)	N 18 9 (50%)	0.785
Plasma, T2: positive viral load	N 53 14 (26.4%)	N 19 12 (63.2%)	0.004

Results: Probability of favorable outcome in patients receiving mAbs by fitting a logistic regression analysis

Parameters	OR	95%CI	p	AOR	95%CI	p
Vaccination: Yes No	 Ref 0.037	 0.005-0.282	 0.001	 Ref 0.065	 0.008-0.525	 0.010
Age, each year more	1.010	0.979-1.041	0.541			
Comorbidities: Age >65 yrs Chronic diseases Immunodeficiencies BMI >30	 0.412 1.545 0.509 0.263	 0.134-1.267 0.335-7.125 0.168-1.545 0.028-2.443	 0.122 0.577 0.233 0.240			
Days from symptom onset to mAb therapy, each day more	0.696	0.575-0.843	<0.001	0.762	0.614-0.945	0.014
Log_{10} NP viral load T0, each cp/mL more	0.939	0.747-1.179	0.588			
Log_{10} saliva viral load T0, each cp/mL more	1.105	0.893-1.367	0.359			
Log_{10} plasma viral load T0, each cp/mL more	1.219	0.961-1.546	0.102			
Plasma viral load at T0: Positive Negative	 Ref 0.514	 0.194-1.362	 0.181	 Ref 0.867	 0.280-2.685	 0.867

Limitations of the study

- Lack of **control group** of unvaccinated and vaccinated patients **not receiving mAbs**
- Few data about viral variant; **small sample size** for sensitivity analyses on fully vaccinated patients, immunocompromised patients, Omicron variant, Sotrovimab
- Lack of **TIXAGEVIMAB/CILGAVIMAB treatment**
- Lack of **neutralizing Ab titers before mAbs treatment**

Conclusions

- **Treatment with mAbs was confirmed safe and effective** in protecting towards diseases progression (no deaths), also in unvaccinated patients receiving mAb.

- Despite featuring higher risk factors and higher plasma SARS-COV-2 RNA, **vaccinated patients receiving mABs were significantly more protected** toward severe outcomes as compared to unvaccinated patients.

- These results emphasize the **importance of prompt and early mAb treatment in high-risk patients** with comorbidities even when vaccinated and need to be confirmed in future studies on current viral variants and mAbs including a control group.

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