Headline results for a Phase 4, 52-week, randomised, double-blind, placebo-controlled study to assess adverse events of special interest (AESI) in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving belimumab

Saira Sheikh,[1] Morton A Scheinberg,[2] Cheng-Chung Wei,[3] Dana Tegzova,[4] William Stohl,[5] Tamara Mucenic,[6] Roger A Levy,[7] Damon Bass,[7] Jorge Ross Terrés,[7*] Raj Punwaney,[7] Julia Harris,[8] Kevin S Thorneloe,[7] Beulah Ji,[8] David Roth[7]

[1]University of North Carolina, Chapel Hill, USA; [2]Centro de Pesquisas Clinicas do Hospital Abreu Sodré, São Paulo, Brazil; [3]Chung Shan Medical University, Taichung City, Taiwan; [4]Institute of Rheumatology, Prague, Czech Republic; [5]University of Southern California Keck School of Medicine, Los Angeles, USA; [6]Hospital Moinhos de Vento, Porto Alegre, Brazil; [7]GSK, Philadelphia, USA; [8]GSK, Uxbridge, UK

**At the time of the study*

Disclosures

- Roger A Levy, Damon Bass, Raj Punwaney, Julia Harris, Kevin S Thorneloe, Beulah Ji and David Roth are employees of GlaxoSmithKline (GSK) and hold shares in the company
- Jorge Ross Terrés was an employee of GSK at the time of study and holds shares in the company
- Saira Sheikh has worked as a paid consultant for GSK
- Cheng-Chung Wei has received research funding from AbbVie, BMS, Celgene, Janssen, Novartis, Pfizer, TSH Biopharm and UCB, and has worked as a paid consultant for AbbVie, BMS, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer, Sanofi-Aventis, TSH Biopharm and UCB
- William Stohl has received research funding from GSK and worked as a paid consultant for Janssen
- Tamara Mucenic has received research funding from Amgen, Eli Lilly, GSK, Janssen, Pfizer and Roche, has worked as a paid consultant for Janssen, Novartis, Roche and UCB, and has been a paid speaker for AbbVie, Janssen, Novartis, Pfizer, Roche and UCB
- Morton A Scheinberg and Dana Tegzova have nothing to disclose
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Background

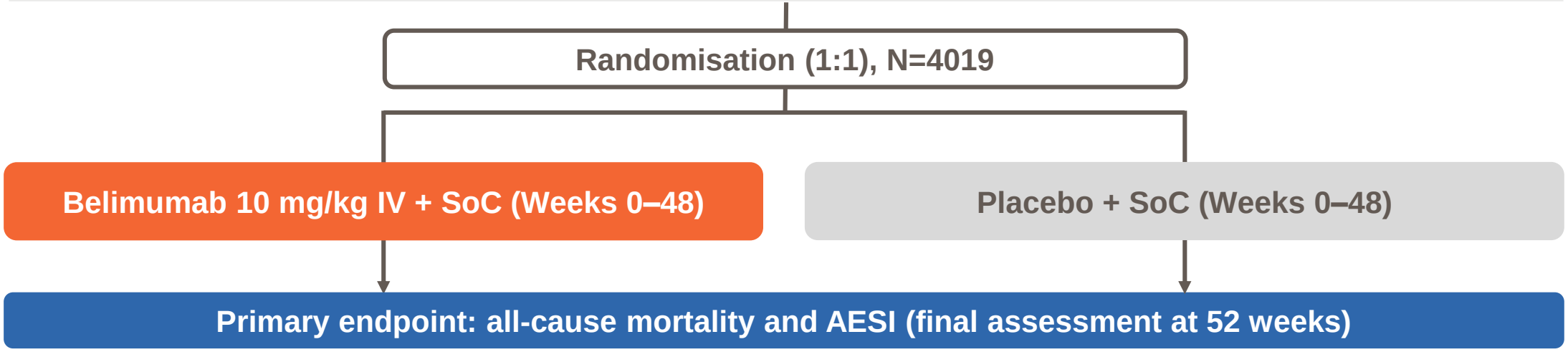
- Belimumab is approved as an add-on treatment for active, autoantibody-positive SLE[1,2]
- Phase 2, Phase 3, and long-term extension studies have shown a favourable benefit-risk profile for belimumab[3-8]
- However, there were numerical differences between belimumab and placebo on background standard of care (SoC), in the incidence of mortality, infections, hypersensitivity reactions and some psychiatric events
- BASE was a 52-week, randomised, double-blind, placebo-controlled safety study to assess these adverse events of special interest (AESI), along with malignancy

Objective: To evaluate all-cause mortality and AESI in adult patients with active, autoantibody-positive SLE receiving IV belimumab or placebo, plus standard of care, over 52 weeks

1. European Medicines Agency. Benlysta EPAR, 2016; 2. Benlysta prescribing information. Rockville (MD): Human Genome Sciences; 2018; 3. Wallace DJ, *et al. Arthritis Rheum* 2009; 61: 1168–78; 4. Furie R, *et al. Arthritis Rheum* 2011; 63: 3918–30; 5. Navarra SV, *et al. Lancet* 2011; 377: 721–31; 6. Stohl W, *et al. Arthritis Rheum* 2017; 69: 1016–27; 7. Zhang F, *et al. Ann Rheum Dis* 2018; 77: 355–63; 8. Wallace DJ, *et al. Arthritis Rheum* 2019; epub ahead of print: doi: 10.1002/art.40861. SLE, systemic lupus erythematosus.

Methods: A multicentre, placebo-controlled safety study

Key selection criteria	
Inclusion • ≥18 years of age • Active, autoantibody-positive SLE • Receiving SLE treatment with steroids, immunomodulators and/or antimalarials	Exclusion • Prior belimumab use • B-cell-targeted therapies in the last year • Other biologic agent within 90 days • Malignant neoplasm in the last 5 years • Required management of acute or chronic infections within 60 days • Severe, active lupus kidney disease or CNS lupus
• No minimum SLE disease activity was required; no exclusion based on previous history of psychiatric conditions	



Dosing: Days 0, 14 and 28, then every 28 days. SoC could include oral cyclophosphamide

AESI, adverse events of special interest; CNS, central nervous system; IV, intravenous; SLE, systemic lupus erythematosus; SoC, standard of care

Methods: Data analyses

Two study periods defined for 52-week analyses

On-treatment (primary analysis):
First dose to last dose + 28 days

On-study (supportive analysis):
On-treatment and off-treatment (i.e. if patient was followed after discontinuing study drug)

- All safety analyses carried out in **as-treated population** (n=4003 randomised and treated)*
- Differences (95% CI) versus placebo were calculated
  - For all-cause mortality and pre-specified AESI
  - *Post hoc* for on-treatment serious suicidal ideation/behaviour and self-injury events (per sponsor adjudication), and on-study suicidal ideation/behaviour (C-SSRS) (pre-specified endpoints)

*All randomised patients who received ≥1 dose of study drug, grouped according to the actual treatment administered for majority of time
AESI, adverse events of special interest; CI, confidence interval; C-SSRS; Columbia-Suicide Severity Rating Scale

Results: Study population

- Baseline demographics and disease characteristics were similar between treatment groups (n=4003)

Baseline characteristics: ITT population*	Belimumab 10 mg/kg IV (n=2001)	Placebo (n=2002)
Age, years, mean (SD)	40.4 (12.8)	40.8 (12.7)
Female, n (%)	1848 (92.4)	1853 (92.6)
SLE disease duration, years, median (range)	5.1 (0–54)	5.3 (0–48)†
SELENA-SLEDAI, n (%) Mean (SD) ≤9, n (%) ≥10, n (%)	 7.8 (4.7)‡ 1363 (68.1) 638 (31.9)	 7.9 (4.5) 1369 (68.4) 633 (31.6)
Low complement and high anti-dsDNA binding, n (%)	568 (28.4)	584 (29.2)

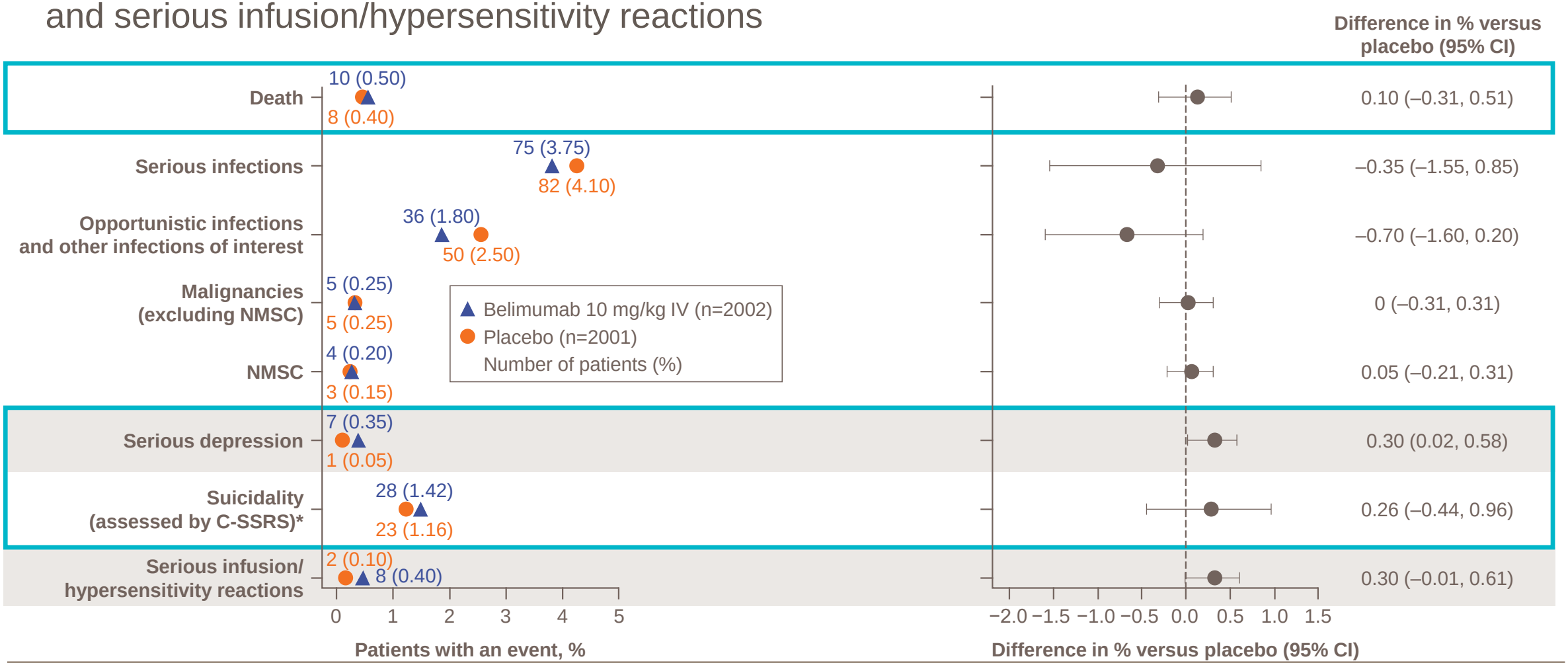
- 258 (12.9%) belimumab and 271 (13.5%) placebo patients withdrew from the study prior to Week 52; the most common reason was withdrawal by patient (6.4% in each group)

*All randomised patients who received ≥1 dose of study drug according to original allocation; one patient was randomised to placebo but incorrectly received belimumab for >50% of doses, so is included in the belimumab arm for safety analyses (as-treated population); †n=2001; ‡n=2000. dsDNA, double-stranded deoxyribonucleic acid; ITT, intent-to-treat; IV, intravenous; SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - SLE Disease Activity Index; SLE, systemic lupus erythematosus

Results: Incidence rates of mortality and protocol-defined AESI

Primary analysis (on-treatment period)

- Overall rates of mortality and AESI were similar between groups, except for serious depression and serious infusion/hypersensitivity reactions



*Treatment-emergent suicidal ideation/behaviour was assessed in patients with ≥1 on-treatment and a pre-treatment C-SSRS assessment (placebo: n=1986, belimumab: n=1972).
AESI, adverse events of special interest; CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale; IV, intravenous; NMSC, non-melanoma skin cancer

Results: All-cause mortality

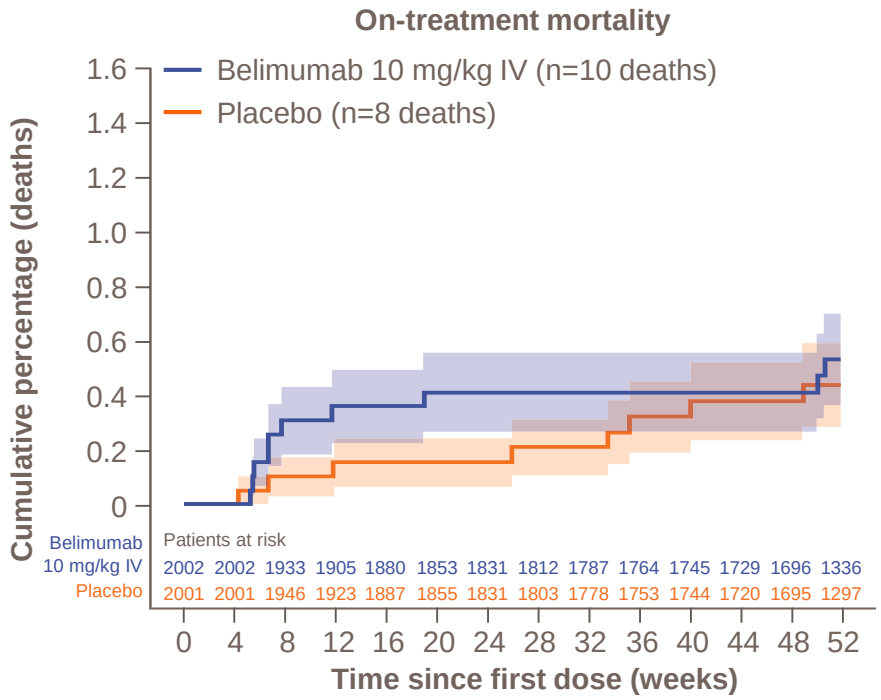
On-treatment deaths

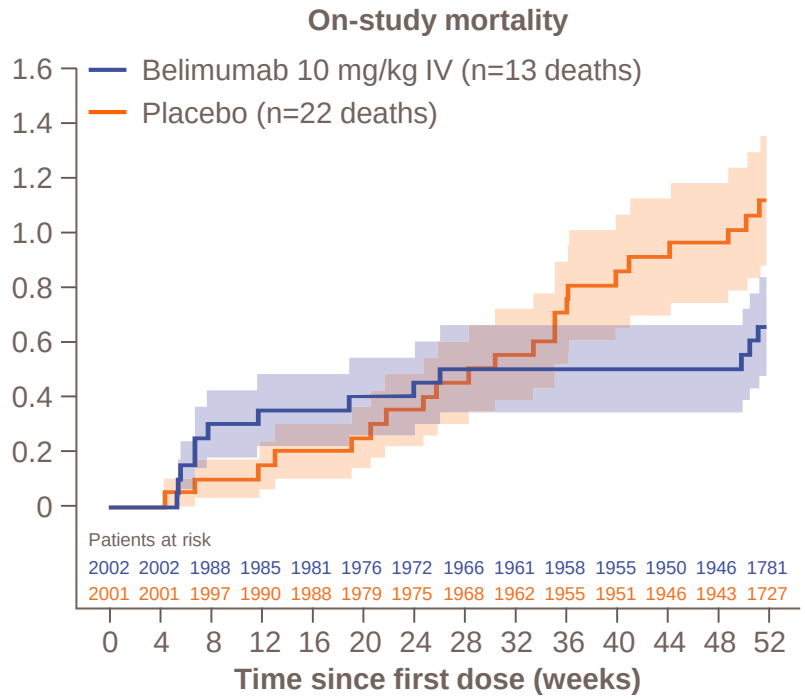
- Occurred in 10 (0.50%) belimumab and 8 (0.40%) placebo patients
  - Difference versus placebo (95% CI): 0.10 (–0.31, 0.51)
- Most frequently infection-related – Belimumab: n=9 (0.45%), placebo: n=3 (0.15%)

On-study deaths

- Occurred in 13 (0.65%) belimumab and 22 (1.10%) placebo patients
  - Difference versus placebo (95% CI): –0.45 (–1.03, 0.13)
- Most frequently infection-related – Belimumab: n=12 (0.60%), placebo: n=8 (0.40%)

On-treatment mortality was similar between groups, with more post-treatment deaths in the placebo group





Shaded regions represent standard error
CI, confidence interval; IV, intravenous

Results: Serious psychiatric events and suicidality

Serious psychiatric events*

- Higher rates of serious depression events for belimumab (7 [0.35%]) versus placebo (1 [0.05%])
  - Difference versus placebo (95% CI): 0.30 (0.02, 0.58)

Number of patients (%)	Belimumab 10 mg/kg IV (n=2002)	Placebo (n=2001)	Difference vs placebo (95% CI) – post hoc
Serious suicidal ideation/behaviour and self-injury, sponsor-adjudicated events	15 (0.75)	5 (0.25)	0.50 (0.06, 0.94)
Suicidal behaviour	4 (0.20)	1 (0.05)	
Suicidal ideation	10 (0.50)	3 (0.15)	
Self-injurious behaviour without suicidal intent	1 (0.05)	1 (0.05)	

On-study C-SSRS assessment

- Suicidal ideation/behaviour occurred in 48/1974 (2.43%) belimumab and 39/1988 (1.96%) placebo patients
  - Difference (95% CI): 0.47 (–0.44, 1.38) (*post hoc* analysis)

Treatment-emergent C-SSRS assessment†

- Suicidality reported for 28/1972 (1.42%) belimumab and 23/1986 (1.16%) placebo patients
  - Difference (95% CI): 0.26 (–0.44, 0.96)

No suicide-related deaths were reported

*On-treatment and on-study rates are the same; †on-treatment C-SSRS: Suicidal ideation/behaviour occurred in 44/1972 (2.2%) belimumab and 37/1986 (1.9%) placebo patients
CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale; IV, intravenous

Conclusions

- This double-blind, placebo-controlled, 4003-patient safety study is the largest SLE clinical study to date

- On-treatment rates were similar between belimumab and placebo for:
  - All-cause mortality
  - Serious infections
  - Opportunistic infections/other infections of interest (serious or non-serious)
  - Malignancy

- Higher rates were observed on belimumab versus placebo for the following events, although the numbers of cases were low:
  - Serious psychiatric events
  - Serious infusion and hypersensitivity reactions

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