Summary of Safety and Clinical Performance

FertiCult Flushing media

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The SSCP is not intended to replace the Instructions For Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to the intended users.

1 Device identification and general information

1.1 Device trade name(s)

- FertiCult Flushing medium without human albumin
  (alternative name in Sil-Select Plus kit: Sil-Select Plus Sperm Washing / Insemination medium without human albumin)
- FertiCult Flushing medium
  (alternative name in Sil-Select Plus kit: Sil-Select Plus Sperm Washing / Insemination medium)
- FertiCult Flushing medium with gentamicin
  (alternative name in Sil-Select Plus kit: Sil-Select Plus Sperm Washing / Insemination medium with gentamicin)
- FertiCult Flushing medium with phenol red
  (alternative name in Sil-Select Plus kit: Sil-Select Plus Sperm Washing / Insemination medium with phenol red)
- FertiCult Flushing medium with phenol red and gentamicin
  (alternative name in Sil-Select Plus kit: Sil-Select Plus Sperm Washing / Insemination medium with phenol red and gentamicin)

Remark: When FertiCult Flushing media are assembled in a kit together with Sil-Select Plus media, the products are marketed under the name "Sil-Select Plus Sperm Washing / Insemination media". However, this does not change anything to the content of the bottles and their intended use. So this SSCP is also applicable for "Sil-Select Plus Sperm Washing / Insemination media".

1.2 Manufacturer's name and address

FertiPro NV
Industriepark Noord 32
8730 Beernem
Belgium

1.3 Manufacturer's single registration number (SRN)

BE-MF-000000313

1.4 Basic UDI-DI

5411967FLUSH1WY

1.5 Medical device nomenclature description/text

Applicable EMDN code: U08020502 (Materials/solutions for preparation/handling for assisted reproduction)

1.6 Class of device

Europe: Class III devices according to Annex VIII of the MDR (Regulation (EU) 2017/745)

1.7 Year when the first certificate (CE) was issued covering the device

FertiCult Flushing medium: 2010

1.8 Authorized representative if applicable; name and the SRN

Not applicable

1.9 Notified Body (NB)'s name and single identification number

BSI Group The Netherlands BV
NB identification number: 2797

2 Intended use of the device

2.1 Intended purpose

FertiCult Flushing media are intended for *in vitro* procedures including washing of human gametes (sperm and oocytes), sperm swim-up procedures, intra-uterine insemination (IUI) of the spermatozoa and intracytoplasmic sperm injection (ICSI). FertiCult Flushing media can also be used for human embryo washing and holding, and for embryo transfer in the uterine cavity.

FertiCult Flushing media are designed to enable in vitro manipulation of gametes and embryos outside the CO_2 incubator.

2.2 Indication(s) and intended patient groups

FertiCult Flushing media:

- are designed for washing of human ova, spermatozoa and embryos
- can be used for swim-up techniques of human spermatozoa
- can be used for the preparation of density gradient media
- can be used for sperm injection in oocytes during ICSI
- can be used for the introduction of washed spermatozoa in the uterus (IUI)
- can be used for embryo transfer

FertiCult Flushing media are used during ART-procedures of patients with infertility problems.

Direct physical contact occurs between the media products and human gametes or embryos. With embryo transfer and IUI, the media come into direct contact with the uterus mucosal membranes of the patient.

2.3 Contraindications and/or limitations

There are no reasonably foreseeable medical conditions for which FertiCult Flushing media are not to be used.

3 Device description

3.1 Description of the device

FertiCult Flushing media are intended for *in vitro* procedures including washing of human gametes (sperm and oocytes), sperm swim-up procedures, IUI of the spermatozoa and ICSI. FertiCult Flushing media can also be used for human embryo washing and holding, and for embryo transfer in the uterine cavity.

As indicated in the IFU of FertiCult Flushing medium without human albumin, it is advised to add human serum albumin (HSA) at a concentration of 4 g/liter. The other media variants are complete and need no further additives. FertiCult Flushing media contain HEPES and are designed to enable *in vitro* manipulation of gametes and embryos outside the CO_2 incubator. The media consist of a balanced salt solution supplemented with carbohydrate energy sources such as glucose, pyruvate and lactate. Additionally, the media are also available with phenol red and/or gentamicin:

- The inclusion of HSA (which is a medicinal substance derived from human blood plasma) in ART media from FertiPro is approved by the EMA (European Medicine Agency).
- The added gentamicin complies with Ph. Eur. Monograph Standard 0331, is EDQM-certified and is approved by the MEB (Medicines Evaluation Board, the competent authority of The Netherlands).

The devices are not intended for single use. Multiple single-procedures can be performed with one bottle of FertiCult Flushing media. The media can be used up to 7 days after bottle opening (when sterile conditions are maintained and the products are stored at 2-8°C).

FertiCult Flushing media are sterilized using aseptic processing techniques (filtration).

3.2 A reference to previous generation(s) or variants if such exist, and a description of the differences

No previous generation of the devices have been brought on the market by FertiPro.

3.3 Description of any accessories which are intended to be used in combination with the device

No accessories for FertiCult Flushing media are identified.

3.4 Description of any other devices and products which are intended to be used in combination with the device

- For FertiCult Flushing medium without human albumin: as indicated in the IFU, FertiPro NV strongly suggests to supplement FertiCult Flushing medium without human albumin with 4.0 g/l human albumin solution before use.
- Sil-Select Plus Sperm Washing/ Insemination media are assembled in a kit together with Sil-Select Plus media (Sil-Select Plus Upper layer and Sil-Select Plus Lower layer).

4 Risks and warnings

4.1 Residual risks and undesirable effects

The only remaining residual risk is the inclusion of HSA in FertiCult Flushing media. A potential risk associated with HSA is the transmission of viral or prion-carried diseases and the batch-to batch variation:

- **Batch-to-batch variation** is still a problem because of the inherent variability in donor blood. Due to this fluctuation, standardization of procedures remains difficult.
  - ↔ For this reason, a mouse embryo assay and a human sperm survival assay are routinely performed as part of the batch release criteria

- Secondly; with the use of a human-derived protein source, a potential risk exists of **transmitting viral or prion-carried diseases**.
  - ↔ HSA is manufactured with a pasteurization procedure that has led to an excellent viral safety record over the 50 years of clinical use. Only Plasbumin-25 or alternatively, Albunorm 25 will be used as a source of albumin, as these products are covered by a valid Plasma Master File, and the EMA has positively evaluated the usefulness, safety and benefit of the inclusion of these products in FertiPro ART-media.
  - ↔ On the other hand, despite the rigorous quality controls, all cell culture media should still be treated as potentially infectious. At present, there is no known test method that can offer full assurance that products derived from human blood will not transmit infectious agents. Direct physical contact occurs between FertiCult Flushing media and human gametes or embryos. With embryo transfer and IUI, the media come into direct contact with the uterus mucosal membranes of the patient. The instructions for use / MSDS clearly warn that the media contains human albumin solution and that protective clothing should be worn.

The major benefit of HSA in FertiCult Flushing media is clear:

- pH regulator
- Osmotic regulator
- Stabilizator of cell membrane
- Nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation

Based on the analysis it is concluded that the benefit of adding HSA to the media outweighs the risk and the overall residual risk related to the use of FertiCult Flushing media with inclusion of HSA has been judged acceptable.

With respect to the above, following information is provided to the customer:

- Product composition is clearly indicated on the labels and instructions for use
- Instructions for use contains the following warning:
  - Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of proven virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes. Therefore, handle all specimens as if capable of transmitting HIV or hepatitis.
  - All blood products should be treated as potentially infectious. Source material used to manufacture this product was tested and found non-reactive for HbsAg and negative for Anti-HIV-1/-2, HIV-1, HBV, and HCV. Furthermore, source material has been tested for

parvovirus B19 and found to be non-elevated. No known test methods can offer assurances that products derived from human blood will not transmit infectious agents.

No other known undesirable side-effects are identified.

4.2 Warnings and precautions

Besides the above, attention should be paid to the following warnings and precautions (as described in the instructions for use):

- Do not use the product if:
  - it becomes discoloured (if medium contains phenol red), cloudy or shows any evidence of microbial contamination
  - seal of the container is opened or defect when the product is delivered
  - expiry date has been exceeded
- Do not freeze before use
- Do not re-sterilize after opening
- Products that include gentamicin should not be used on a patient that has a known allergy to gentamicin or similar antibiotics
- Depending on the number of procedures that will be performed on one day, remove the required volume of medium under aseptic conditions in an appropriate sterile recipient. This is in order to avoid multiple openings/warming cycles of the medium. Discard excess (unused) media.
- Keep away from (sun)light
- Aseptic technique should be used to avoid possible contamination even when the product contains gentamicin
- Always wear protective clothing when handling specimens.
- Any serious incident (as defined in European Medical Device Regulation 2017/745) that has occurred should be reported to FertiPro NV and the competent authority of the Member State in which the user and/or patient is established.

4.3 Summary of any field safety corrective action (FSCA including FSN) if applicable

No field safety corrective actions with regard to FertiCult Flushing media were needed.

5 Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1 Real-world evidence analyses

A literature search is performed to investigate whether embryological and/or clinical ART outcomes obtained during literature search are consistent with the embryological competency limits and/or with the clinical ART outcomes described in the benchmark papers from the ESHRE (see tables below).

The Vienna consensus report published in 2017 is the result of a 2 day consensus meeting of expert professionals from Sweden, Turkey, UK, Australia, Italy, Spain, Belgium, Austria, Ireland, Canada, USA, and Norway. As a starting point for the discussion, two surveys were organized to collect information on indicators used in IVF laboratories worldwide. During the meeting, the results of the surveys, scientific evidence (where available), and personal clinical experience were integrated into presentations by experts on specific topics. After presentation, each proposed indicator was discussed until consensus was reached within the panel (ESHRE Special Interest Group of Embryology 2017).

The following competency limits concerning embryological outcomes are reported by the expert group:

Competency limits reported by the ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine in 2017. The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators (ESHRE Special Interest Group of Embryology 2017)	ICSI normal fertilization rate: **≥65%** (lower range: 60%) IVF normal fertilization rate: **≥60%** (lower range: 50%) ***Since multiple factors can have an influence on the embryology outcomes, (ART policy, approach of the clinic, patients characteristics), a value 10% lower than the competency limit is acceptable.***

Each year, the ESHRE publishes a peer-reviewed report, which collects, analyses and reports ART data generated in Europe. The most recent report includes data from 1382 institutions in 39 countries, with a total of 940 503 treatment cycles (covering the time period from 1 January to 31 December 2017) (Wyns et al. 2021) and data is summarized in the table below.

ART in Europe, 2017: results generated from European registries by ESHRE A total of 940 503 treatment cycles, involving 165 379 with IVF, 391 379 with ICSI, 271 476 with frozen embryo replacement (FER), 37 303 with preimplantation genetic testing (PGT), 69 378 with egg donation (ED), 378 with IVM of oocytes and 5210 with FOR (frozen oocyte replacement) were recorded. European data on IUI using husband / partner's semen (IUI-H) and donor semen (IUI-D) were reported from 1197 institutions offering IUI in 29 countries and 24 countries, respectively. A total of 162 948 treatments with IUI-H and 50 467 treatments with IUI-D were included.	**In vitro fertilization (IVF):** Clinical pregnancy rate per aspiration: **28.3%** *(range: 21.0 – 42.3%)* Clinical pregnancy rate per transfer: **36.2%** *(range: 28.4 – 47.1%)* Delivery rate per aspiration: **21.5%** *(range: 10.4 – 40.9%)* Delivery rate per transfer: **27.5%** *(range: 11.2 – 41.5%)*	**Intra cytoplasmic sperm injection (ICSI):** Clinical pregnancy rate per aspiration: **26.3%** *(range: 18.4 – 38.2%)* Clinical pregnancy rate per transfer: **35.2%** *(range: 27.4 – 45.1%)* Delivery rate per aspiration: **20.2%** *(range: 12.2 – 36.8%)* Delivery rate per transfer: **26.8%** *(range: 17.5 – 37.4%)*	**Frozen embryo replacement (FER):** Pregnancy rate per thawing: **34.4%** *(range: 22.0 – 49.1%)* Pregnancy rate per transfer: **35.3%** (range: 23.5 – 51.3%) Delivery rate per thawing: **23.3%** *(range: 3.2 – 37.8%)* Delivery rate per transfer: ***24.3%*** *(range: 3.2 – 38.6%)*	**Intrauterine insemination(IUI):** **using husband semen (IUI-H):** Delivery rate per cycle: **8.8%** *(range: 4.2 - 24.4%)* **using donor semen (IUI-D):** Delivery rate per cycle: **13.8%** *(range: 4.3 – 42.0%)*
	Since multiple factors can have an influence on the ART outcomes (ART policy, approach of the clinic, patients characteristics), a value within the range of the ESHRE value is acceptable.			

As there are no alternative treatment options that can be used for gamete/embryo washing/handling and ART procedures, all data included in the ESHRE report are generated using FertiCult Flushing media or a similar device available on the market. Reported outcomes in the benchmark paper can therefore be considered as benchmark data for ART procedures. Nevertheless, when comparing clinical data, one should be aware that:

- During ART processes, gametes/embryos come into contact with several (other) ART media and undergo a lot of manipulations that all can have an influence on the reported outcomes.
- Depending on the patient characteristics, different outcomes can be obtained.

The articles studying the performance of FertiCult Flushing medium are indicated in the table below. Overall, it can be concluded from these papers that embryological and/or clinical ART outcomes when FertiCult Flushing medium is used for gamete/embryo washing and handling, swim-ups, density gradient preparation, or during IVF, ICSI, IUI are consistent with the embryological competency limits (ESHRE

Special Interest Group of Embryology 2017) and/or with the published ART outcomes as reported by the ESHRE (Wyns et al. 2021), suggesting a safe and adequate performance of FertiCult Flushing medium.

Papers describing the use of FertiCult Flushing media ***for washing ova, spermatozoa and embryos***
(Benchaib et al. 2007)
(Frydman et al. 2008)
(Huang et al. 2005)
(Fauque et al. 2010)
(Benchaib et al. 2005)
(Le Du et al. 2005)
(Barraud-Lange et al. 2011)
(Pont et al. 2012)
(Falah et al. 2014)
(Desch et al. 2015)
(Jansen et al. 2017)
(Le Bras et al. 2017)
(Llabador et al. 2015)
(Philippon et al. 2015)
(Fournier et al. 2018)
(Hachemi et al. 2019)
(Delaroche et al. 2021)
(Mayeur et al. 2020)
(Puy et al. 2020)
(Cil et al. 2022)
(Hachemi et al. 2021)
Papers describing the use of FertiCult Flushing media ***for sperm injection in oocytes during ICSI***
(Ledee et al. 2008)
(Ledee et al. 2010)
(Abbas et al. 2020)
Papers describing the use of FertiCult Flushing media ***for the introduction of washed spermatozoa in the uterus (IUI)***
(Barraud-Lange et al. 2011)
(Pont et al. 2012)
(Jansen et al. 2017)
(Vichinsartvichai, Traipak, and Manolertthewan 2018)
(Vichinsartvichai et al. 2015)
(Ruiter-Ligeti et al. 2020)
Papers describing the use of FertiCult Flushing media ***for the preparation of density gradient***
(El Khattabi et al. 2013)
Papers describing the use of FertiCult Flushing media ***for washing ova, spermatozoa and embryos AND for the preparation of density gradient***
(Dupont et al. 2015)
(Sifer et al. 2014)
(Herbemont et al. 2017)
(Vichinsartvichai, Traipak, and Manolertthewan 2018)
(Vichinsartvichai et al. 2015)
(Gonzalez-Ravina et al. 2022)
Papers describing the use of FertiCult Flushing media ***for other purposes***
(Buffat et al. 2006)
(Parmegiani et al. 2012)
(Beauvillard et al. 2015)

5.2 Device registers

In addition, clinical data is obtained from IVF centers in Europe that use FertiCult Flushing medium. ART outcomes of these clinics are consistent with clinical outcomes described in national public registers of the countries in which the IVF centers are located or with the ART outcomes as described in the benchmark paper from the ESHRE (Wyns et al. 2021). The outcomes can be considered as benchmark data, as these national outcomes are generated with FertiCult Flushing media or a similar devices available on the market.

IUI outcomes from the years 2017 and 2018 of two IVF clinics located in Europe (details are confidential) are included in the clinical evaluation report of FertiCult Flushing medium. It could be concluded that the IUI results of these IVF clinics are consistent with clinical outcomes described in the national public registers of the country. Also ART outcomes from an IVF center in the Netherlands generated between 2013 to 2021 are consistent with the national outcomes. Next, ART outcomes of 2666 IVF/ICSI procedures performed in 2018 and 5671 IVF/ICSI procedures performed in 2019 (>80% of the procedures are ICSI) generated in 5 clinics in an European country (details are confidential) are consistent with the outcomes reported in the benchmark ESHRE article. This all indicates a good and safe performance of FertiCult Flushing medium.

5.3 Analysis complaint, customer/market feedback, vigilance

No additional actions were initiated, based on the cumulative nature and/or occurrence of all complaints, customer/market feedback and vigilance (if any) during the PMCF analysis.

5.4 An overall summary of the clinical performance and safety

FertiCult Flushing media functions as stated by the manufacturer: i.e. FertiCult Flushing media supports *in vitro* procedures involving human gametes (sperm and oocytes), including washing of gametes, sperm swim-up procedures, IUI of the spermatozoa and ICSI. FertiCult Flushing media can also be used for human embryo washing and holding, and for embryo transfer in the uterine cavity.

This is established by clinical data obtained during literature search which demonstrate that embryology and/or ART outcomes of procedures in which FertiCult Flushing medium is used, are consistent with the competency limits reported by the Vienna consensus group (ESHRE Special Interest Group of Embryology 2017) and/or with the published ART outcomes as reported by the ESHRE (Wyns et al. 2021). In addition, clinical data from multiple IVF centers in Europe show that ART outcomes of procedures in which FertiCult Flushing medium is used, are consistent with published national ART outcomes in the country where the IVF clinic is located or are consistent with the published outcomes as reported by the ESHRE (Wyns et al. 2021).

Moreover, there is no evidence from the clinical data, as well as from the registered complains, market/customer feedback and/or vigilance that FertiCult Flushing media is toxic for gametes and embryos, nor that the media have no risk for mutagenity, oncogenicity, teratogenity, carcinogenity, cytotoxicity, allergenicity and irritancy for patients and users. Furthermore, no infrequent complications or problems were detected.

5.5 Ongoing or planned post-market clinical follow-up

Post-market clinical follow-up for FertiCult Flushing media (including PMCF for the HSA and gentamicin component included in FertiCult Flushing media) will be performed at least yearly.

This Summary of Safety and Clinical Performance will be updated with information from the post-market clinical follow-up, if this is needed to ensure that any clinical and/or safety information described in this document remains correct and complete.

6 Possible diagnostic or therapeutic alternatives

Several devices as FertiCult Flushing media with a similar intended use are available on the European Union or international markets. Besides these, there are no other alternative treatments that can be used in gamete/embryo washing and/or handling and ART procedures.

7 Suggested profile and training for users

FertiCult Flushing media are used in specialized laboratories performing fertilization techniques, including IVF, ICSI and sperm preparation/analysis. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

8 Reference to any applicable common specification(s), harmonized standard(s) or applicable guidance document(s)

The following guidance document was used:

- **MDCG 2019-9**: Summary of safety and clinical performance A guide for manufacturers and notified bodies (August 2019).

The following technical standards apply to FertiCult Flushing media:

- **MDR 2017/745:** European Medical Device Regulation 2017/745 of 5 April 2017
- (EN) ISO 13485:2016 / EN ISO13485:2016/Ac:2018: Medical devices — Quality management systems — Requirements for regulatory purposes
- **EN 556-2:2015:** Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' –Requirements for aseptically processed medical devices
- **(EN) ISO 20417:2021:** Medical Devices: information supplied by the manufacturer
- **ISO 10993-1:2018 / EN ISO 10993-1:2020:** Biological evaluation of medical devices -- Part 1: Evaluation and testing
- **(EN) ISO 10993-3:2014:** Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.
- **(EN) ISO 10993-5:2009:** Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity
- **ISO 10993-10:2010 / EN ISO 10993-10:2013:** Biological evaluation of medical devices -- Part 10: Tests for irritation and delayed-type hypersensitivity
- **(EN) ISO 10993-18:2020:** Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process
- **(EN) ISO 10993-23:2021:** Biological evaluation of medical devices – Part 23: Tests for irritation
- **ISO 13408-1:2008 (Amd 1:2013) / EN ISO 13408-1:2015:** Aseptic processing of health care products – Part 1: general requirements
- **(EN) ISO 13408-2:2018:** Aseptic processing of health care products – Part 2: Filtration.
- **ISO 13408-6:2005 (Amd 1:2013) / EN ISO 13408-6:2011:** Aseptic processing of health care products – Part 6: Isolator systems
- **ISO 14644-1:2015:** Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration
- **(EN) ISO 14644-3:2019:** Cleanrooms and associated controlled environments - Part 3: Test methods
- **(EN) ISO 14971:2019:** Medical devices – Application of risk management to medical devices

- **ISO 15223-1:2021 / EN ISO 15223-1:2016:** Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
- **(EN) ISO 17665-1:2006:** Sterilization of health care products – Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
- **ISO 23640:2011 / EN ISO 23640:2015:** In vitro diagnostic medical devices: Evaluation of stability of in vitro diagnostic reagents (Applicable with exclusion of the following sections: No standard is available for the evaluation of stability of Medical Devices, therefore this standard is used as guideline for the set-up of the stability testing in line with the EU list of harmonized standards drafted in support of Council Directive 93/42/EEC and MDR 2017/745)
- **IEC 62366-1:2015 (Amd 1:2020):** Medical devices - Part 1: Application of usability engineering to medical devices
- **NBOG BPG 2014-3:** Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System
- **EMA/CHMP/578661/2010 rev.1:** EMA recommendation on the procedural aspects and dossier requirements for the consultation to the EMA by a notified body on an ancillary medicinal substance or an ancillary human blood derivate incorporated in a medical device or active implantable medical device
- **ISO 22442-1: 2020 / EN ISO 22442-1:2020:** Medical Devices utilizing animal tissues and their derivatives: Part 1: Application of risk management

9 Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
A.1	28/01/2020	Initial version	
A.2	22/09/2020	Revision upon MDR conformity assessment review round 2 by BSI	Date: 16/03/2022 Validation language: English
A.3	05/07/2021	Update 2021	Date: on 12/04/2022 provided to Notified Body for validation Validation language: English
A.4	14/06/2022	Update 2022	Date: 27/06/2022 provided to Notified Body Validation language: English

10 Summary of the safety and clinical performance of the device intended for patients

A summary of the safety and clinical performance of the device intended for patients, is not applicable as the device is for professional use only.

11 References

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