Australian Government
Department of Health
Therapeutic Goods Administration

Nonclinical Evaluation Report

SARS-CoV-2 rS (NVX-CoV2373) [NUVAXOVID®]

Submission No: PM-2021-00623-1-2
Sponsor: Biocelect Pty Ltd

June 2021 – Interim report
October 2021 – Product information submission
December 2021 – Interim report (S31 response)
January 2022 – Final report

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New vaccine
Sponsor: Biocelect Pty Ltd
Generic name: **SARS-CoV-2 rS (NVX-CoV2373)**
Trade name: **NUVAXOVID®**
Dose form and strength: Solution for IM injection; 5 µg
Vaccine Type: Recombinant viral vaccine

Submission No: PM-2021-00623-1-2
Tox file No: E21-233938
TRIM reference: D21-2247953

Evaluator: s22 [redacted]

Date authorised: 24 June 2021 — Interim report
01 October 2021 — Product Information submission
09 December 2021 — Interim report (S31 response)
03 January 2022 — Final report
12 January 2022 — Error and omission

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SUMMARY

- Biocelect Pvt Ltd has applied for provisional registration of a new vaccine, SARS-CoV-2 rS (NVX-CoV2373) (NUVAXOVID®), a SARS-CoV-2 recombinant (r) spike (S) protein antigen (SARS-CoV-2 rS) with Matrix-M1 adjuvant. SARS-CoV-2 rS is proposed to be used for the prevention of mild, moderate, and severe disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proposed dosing regimen involves 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) is given on Days 0 and 21 intramuscularly (IM).
- The Sponsor has generally conducted adequate studies on pharmacology and toxicity of the vaccine and its adjuvant Matrix-M1 (novel excipient containing purified saponins extracted from *Quillaja saponaria*). All repeat-dose toxicity, genotoxicity and reproductive toxicity studies for the vaccine and adjuvant were performed under GLP conditions. No pharmacokinetic studies were conducted with the antigen or the adjuvant. One tissue distribution study with the adjuvant is planned.
- SARS-CoV-2 rS vaccine (i.e., SARS-CoV-2 rS antigen + Matrix-M1 adjuvant) was found to be immunogenic in nonclinical studies in mice, rats, hamsters, rabbits and non-human primates (NHP). SARS-CoV-2 rS vaccine induced both humoral (anti-S, hACE2 receptor binding blocking and virus neutralising antibodies) and cellular immune (Th-1 biased) response in mice and NHP.
- One or two boost immunisations ~10 months following primary immunisation with a different SARS-CoV-2 S protein variant (SA B.1.351 + Matrix-M1), induced strong humoral and cellular immune response against at least three SARS-CoV-2 S protein variants in baboons.
- s47 [redacted]
- The vaccine provided some protection from infection in mice, hamsters and primates when challenged after two immunisation doses, based on viral RNA and subgenomic RNA load and lung histopathology. The immunisation regimen in monkeys was identical to the proposed clinical immunisation regimen (5 µg SARS-CoV-2 rS +50 µg Matrix-M1, 2 IM doses, 21 days apart).
- Lung histopathological changes were less severe in challenged immunised primates compared to challenged controls. Primates do not show SARS-CoV-2 infection-related clinical signs and generally develop only mild lung pathology. There were no studies on protection of older animals from SARS-CoV-2 infection. *In vivo* primary pharmacology studies were of short term; two long term immunogenicity studies are still ongoing.
- No enhanced lung pathology was evident in immunised, virus challenged animals. Findings in a repeat-dose toxicity study with SARS-CoV-2 rS ± Matrix-M1 by the IM route in rabbits showed local reactions at the injection site and elevated serum levels of fibrinogen, C–Reactive protein and globulin in plasma. While no effects on draining lymph node and spleen were observed in the rabbit with SARS-CoV-2 rS ± Matrix-M1, hyperplasia, plasmacytosis and heterophil infiltrates in draining lymph node and/or spleen were observed in rats and rabbits treated with Matrix-M1 with or without an antigen. All the findings were related to immune response to the vaccine and adjuvant and fully or partially reversible a few weeks after the last treatment. Both the SARS-CoV-2 rS vaccine and the Matrix-M1 adjuvant alone were well tolerated.
- Matrix-M1 was negative in two GLP-compliant *in vitro* genotoxicity tests (Ames test and mammalian cell micronucleus test in Chinese Hamster Ovary cells). No *in vivo* genotoxicity study was performed. This is considered acceptable as it was negative in in vitro assays, and the saponin fractions are plant-derived and are approved food additives.

- In a combined reproductive and developmental toxicity study with SARS-CoV-2 rS + Matrix-M1, and Matrix-M1 alone female fertility, embryofetal development and postnatal development of offspring were unaffected.

CONCLUSIONS AND RECOMMENDATION

- SARS-CoV-2 rS + Matrix-M1 elicited both humoral and cellular immune responses to the spike (S) antigen in mice, hamsters and non-human primates and conferred some protection from SARS-CoV-2 infection.
    - Primary pharmacology studies investigating the potential long-term immunity following immunisation with SARS-CoV-2 rS + Matrix-M1 adjuvant vaccine in non-human primates are still ongoing. In baboons, one or two boost immunisations (21 days apart) – with a different SARS-CoV-2 antigen (beta variant) – 10 months following primary immunisation induced rapid and strong immune response against SARS-CoV-2 US-WA1, SA B1.351 and UK B.1.1.7 variants.
- Repeat–dose toxicity studies with the proposed vaccine in rabbits and Matrix-M1 in rats and rabbits raised no safety issues. Treatment–related findings were limited to immune response-related effects.
- SARS-CoV-2 rS + Matrix-M1 did not adversely affect female fertility, embryofetal development or postnatal development in rats. Pregnancy category B1 is considered appropriate.
- Matrix-M1 was not genotoxic.
- All safety studies were conducted with Discovery or EBSI batches. While mouse immunogenicity studies showed comparability between Discovery, SKBio, FDBU and EBSI batches, there are no immunogenicity and safety studies to demonstrated comparability between the commercial batches to be marketed in Australia and the nonclinical batches.
- There are no nonclinical objections to the provisional approval of this vaccine provided Module 3 data showed comparability between nonclinical and commercial batches and/or efficacy and safety have been adequately demonstrated by clinical data for the commercial batches.
- The ongoing immunogenicity studies and planned tissue distribution study should be provided for review once they are completed.
- The draft Product Information should be amended as directed on pages 17–19.

ASSESSMENT

Biocelect Pty Ltd has applied for provisional registration of a new COVID-19 vaccine (also known as NVX-CoV2373 or Novavax COVID-19 Vaccine) (Nuvaxovid®). The vaccine consists of a recombinant (r) spike (S) protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as SARS-CoV-2 rS, as the antigen and Matrix-M1 as the adjuvant. It is indicated for the active immunisation for the prevention of mild, moderate, and severe disease caused by SARS-CoV-2 in adults ≥18 years of age. The proposed dosing regimen is 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) given on Days 0 and 21 intramuscularly (IM). ~~Biocelect Pty Ltd has applied for provisional registration of a new COVID-19 vaccine (also known as NVX-CoV2373 or Novavax COVID-19 Vaccine) (Nuvaxovid®). The vaccine consists of a recombinant (r) spike (S) protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as SARS-CoV-2 rS, as the antigen and Matrix-M1 as the adjuvant. It is indicated for the active immunisation for the prevention of mild, moderate, and severe disease caused by SARS-CoV-2 in adults ≥18 years of age. The proposed dosing regimen is 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) given on Days 0 and 21 intramuscularly (IM).~~

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General comments

SARS-CoV-2 rS vaccine is an adjuvanted recombinant full-length SARS-CoV-2 spike glycoprotein vaccine. This vaccine does not contain live virus.

Module 4 comprised of nonclinical studies with the clinical formulation and the adjuvant with other vaccine antigens. Reports of all completed studies have been provided. Two immunogenicity studies and one tissue distribution study are ongoing, and the absence of these studies do not preclude provisional approval of the vaccine.

The adjuvant, Matrix-M1 consists of purified saponin fractions, cholesterol, and phospholipid and is a new excipient. Since the saponin fractions were plant-derived, they consist of a number of structurally related saponins and the amount of each saponin component may vary between batches. The potential effect of the variation of each saponin component on Matrix-M1 safety and/or efficacy has been addressed by the Sponsor. Overall, the variability in saponins in the purified saponin fractions is not considered to considerably affect Matrix-M1 and the adjuvanted vaccine safety and efficacy (see Section 1.6).

Pharmacology

SARS-CoV-2 is a single-stranded RNA-enveloped virus. Its surface is covered by a large number of trimeric spike (SAR-CoV-2 S) glycoproteins (Figure 1A). SARS-CoV-2 S protein comprises two functional subunits responsible for binding to host cell receptors (S1) and for fusion of virus and host cell membranes (S2). Cleavage by furin-like proteases between S1 and S2 subunits has been shown to be essential for the S-protein mediated cell-cell fusion and viral infectivity (Örd *et al.,* 2020). The proposed SARS-CoV-2 rS vaccine is constructed from the full-length, wild-type SARS-CoV-2 S, where the *S* gene was modified by mutation of the furin cleavage site (Figure 1B) to make it resistant to furin-like protease cleavage.

In prefusion state, SARS-CoV-2 S protein alternates between "open" and "close" conformations (Ke *et al.,* 2020; Figure 1C). When in the "open" conformation, SARS-CoV-2 S protein receptor-binding domain (RBD) binds human angiotensin-converting enzyme 2 (hACE2) (Berger & Schaffitzel, 2020; Ke *et al.,* 2020). SARS-CoV-2 S protein RBD has been shown to be a target antigen for neutralising antibodies (Yuan *et al.,* 2020). In the proposed SARS-CoV-2 vaccine, two proline amino acid substitutions were inserted within the heptapeptide repeat 1 (HR1) domain (B) to stabilise

SARS-CoV-2 S in a prefusion conformation; therefore, the proposed SARS-CoV-2 rS vaccine is expected to optimise presentation of SARS-CoV-2 S protein RBD neutralising epitopes.

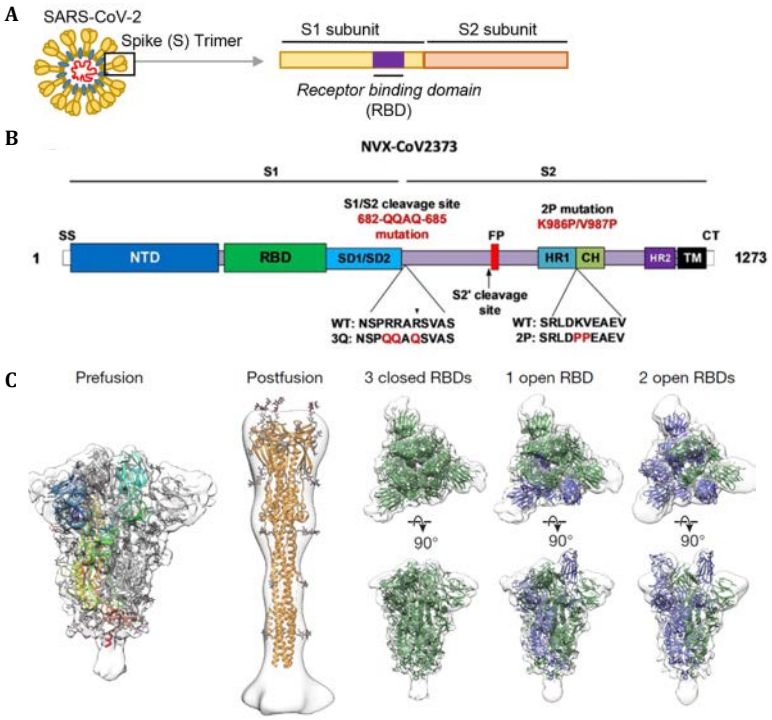

Figure 1. SARS-CoV-2 S structure and the spike protein construct (reproduced from Ke *et al.,* 2020; Tian *et al.,* 2020 & 2021)
CH = central helix; CT = cytoplasmic tail; FP = fusion peptide; HR = heptapeptide repeat; NTD = N-terminus domain; SD = subdomain; SS = signal sequence; TM = transmembrane domain

Primary pharmacology

Pharmacology studies were performed in mice (BALB/c), hamsters, baboons and macaques (cynomolgus and rhesus). Immunogenicity data was overall similar between laboratory species, i.e., high levels of anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibody titres and positive cellular responses in immunised animals. Prime–boost vaccine regimen increased protection against SARS-CoV-2 infection (shown by decreased viral load). Matrix-M1 adjuvant significantly increased vaccine immunogenicity. A Th1-biased immune response was observed in mice, baboons and macaques. No evidence of vaccine-elicited disease enhancement were observed in any of the protection studies. There were no studies on protection in older animals from SARS-CoV-2 infection or lon- term protection following immunisation. The proposed clinical dose SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose), immunisation interval (Days 0 and 21) and route of administration (IM) were studied in baboons and macaques.

Matrix-M1 mechanism of action

The adjuvant, Matrix-M1 is composed of Matrix-A (85%) and Matrix–C (15%), which are ~40 nm nanoparticles of saponin Fraction–A and –C, respectively, extracted from the tree Quillaja saponaria Molina, cholesterol and phospholipid. S47

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Immunogenicity

SARS-CoV-2 rS + Matrix-M1 vaccine was found to be immunogenic in mice, rats, hamsters, rabbits, and non-human primates (NHP - baboons, cynomolgus and rhesus macaques). The presence of Matrix-M1 adjuvant in SARS-CoV-2 rS vaccine increased its immunogenic response in mice or baboons *cf.* SARS-CoV-2 rS alone or vaccines + other adjuvant. A booster dose with Matrix-M1 adjuvant 21 days after the first dose markedly increased the humoral immune response (anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibodies) in mice and NHP. There was high correlation between anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibodies in multiple animal species including NHP.

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s47 Altogether, this indicates that SARS-CoV-2 rS + Matrix-M1 induce predominantly a Th1 driven immune response.

Similar findings were observed in NHP.s47

Overall, immunisation with SARS-CoV-2 rS + Matrix-M1 induced both humoral and cellular immune responses. The immune responses were Th1-biased. Two doses with a booster dose of 3-4 weeks after the first dose and the antigen dose of 5 µg + 50 µg Matrix-M1 as the adjuvant appear to be the optimal immunisation regimen. Increasing the antigen dose to 25 µg did not significantly increase immune responses.s47 . A single boost immunisation, 10 months following primary immunisation induced strong and anamnestic antibody and cellular response.

SARS-CoV-2 rS + Matrix-M1 adjuvant also elicited immune responses in hamsters (anti-S, hACE2 receptor inhibiting and neutralising antibodies), rabbits (anti-S IgG) and rats (anti-S IgG) as investigated in primary pharmacology protection studies, repeat-dose toxicity studies, reproductive and developmental studies, respectively.

Immunogenicity comparison of drug substance (antigen) and drug product batches

Several SARS-CoV-2 rS drug substance (DS) and drug product (DP) produced by different manufacturers (Novavax [Discovery], Emergent BioSolutions, FUJIFILM Diosynth Biotechnologies, PAR Pharmaceuticals, and SK Bioscience), at different manufacturing scale with various purity and particle size were tested to evaluate their immunogenic potential in mice. All animals were immunised with two doses of SARS-CoV-2 rS + Matrix-M1 IM, 14 days apart (*cf.* 21 days apart for the clinical immunisation regimen). The Matrix-M1 batches tested were manufactureds47 The SARS-CoV-2 rSs47 and were mixed withs47

Overall, all batches tested induced an immunogenic response (measured by anti-S and hACE2 receptor inhibiting antibody titres up to 28 days post initial immunisation).s47 SARS-CoV-2 rss47 did not significantly affect the immunogenicity of the vaccine. However, it should be noted that the following parameters/variables have not been tested:

- The long-term immunogenic response;
- The effect of SARS-CoV-2 rS batch variability on cell-mediated immune response;
- The proposed clinical dose (5 µg) and dosing interval (3 weeks);
- Pharmacokinetic and safety profile of the vaccine particle size;
- Most importantly, commercial batches manufactured at s47

Protection against infection

SARS-CoV-2 rS + Matrix-M1 provided protection against SARS-CoV-2 challenge in mice (transiently transfected with hACE2), hamsters and macaques (cynomolgus and rhesus) after two immunisation doses.

In challenged mice immunised with a single dose of s47 a dose-dependent reduction in lung virus titre was observed. No viral load was detected in the lungs of animals immunised with the highest dose of adjuvanted vaccine.

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No clinical signs were observed in challenged, unimmunised cynomolgus macaques which is consistent with other studies in SARS-CoV-2-infected NHP (Muñoz-Fontela et al. 2020) s47

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The predominant Th1-biased response observed in mice and primates suggests low risk of antibody-dependent enhancement (ADE) and vaccine-associated enhanced respiratory disease (VAERD) (for

review see Munoz *et al.,* 2021). In addition, no enhanced lung pathology was evident in immunised, virus challenged animals.

The pharmacology studies indicated that SARS-CoV-2 rS + Matrix-M1 induces humoral (measured by anti-S IgG, hACE2 receptor inhibiting antibodies and virus-neutralising antibodies) and cellular (characterised by a predominant $CD4^+$ Th1 T-cell response) immune responses in mice and NHP. The vaccine protected mice, hamsters and NHP from infection when challenged s47 days after the 2nd vaccine dose, respectively. Only the vaccine doses given to primates were identical to the proposed clinical dosing regimen. There were no studies on protection of older animals from SARS-CoV-2 infection. Pharmacology studies on the duration of protection after immunisation are still ongoing.s47 . According to the EMA evaluation, the rhesus macaque study will cover homologous protection against the WA-1 isolate as well as heterologous protection against the antigenically divergent Brazilian isolate, and the baboon study will include immunogenicity data following boosting with an updated immunogen based on the South African virus variant. These studies will be reviewed once the study reports are available.

Is the vaccine effective against all variant SARS-CoV-2 viruses?

During the course of the pandemic, mutations have arisen in SARS-CoV-2 S protein that has become dominant amongst viruses sequenced from patient samples. It should be noted that SARS-CoV-2 rS + Matrix-M1 vaccine induced the production of wild-type virus neutralising antibodies. No nonclinical data on the efficacy against SARS-CoV-2 variants were provided.

A published study showed that serum samples from recipients of NVX-CoV2373 neutralised the B.1.1.7 variant, albeit at moderately reduced levels (~2-fold) (Shen *et al.,* 2021).

Safety pharmacology

Limited safety pharmacology parameters e.g. body temperature were investigated in the repeat-dose toxicity studies, in accordance with the WHO guideline on nonclinical evaluation of vaccines (2005)[1].

Pharmacokinetics

No pharmacokinetic studies were conducted. No pharmacokinetic studies are generally required for vaccine antigens in accordance with the WHO guideline on nonclinical evaluation of vaccines (2005). However, tissue distribution of adjuvants may be of value as recommended by the WHO guidelines on the nonclinical evaluation of vaccine adjuvants (2013)[2] and EMA guideline on adjuvants in vaccines for human use (2005)[3].

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[1] WHO guidelines on nonclinical evaluation of vaccines (2005)
[2] WHO guidelines on the nonclinical evaluation of vaccine adjuvants (2013)
[3] Guideline on adjuvants in vaccines for human use (2005)

Toxicity

Acute toxicity

No single-dose toxicity studies were performed with the SARS-CoV-2 rS and/or Matrix-M1 adjuvant. This is acceptable, with relevant information on acute toxicity available from repeat-dose toxicity studies instead, which are discussed below.

Repeat-dose toxicity

A 36–day GLP compliant repeat–dose toxicity study (Study 2088-20035) was conducted in rabbits using the IM route of administration with the clinical candidate vaccine, SARS-CoV-2 rS ± Matrix-M1. s47 [redacted]

The dosing interval is considered adequate given that high antibody titres were detected after booster doses. Use of a single species (rabbits) is consistent with the relevant guidelines and demonstration of good immunogenicity supports the use of this species as an appropriate animal model for the toxicity study. Adequate number of animals were used in the study (10/sex/treatment group with 5/sex sacrificed after 3 doses and 5/sex after 4 doses, plus 5/sex/group for recovery observations).

As toxicokinetic data for the adjuvant were not obtained in the repeat–dose toxicity studies, animal to human exposure comparisons have been made based on body surface area adjusted doses (Table I). In the pivotal repeat–dose toxicity study in rabbits, Matrix-M1 (plus SARS-CoV-2 rS; no adjuvant only group) was s47 [redacted]

Table I. s47

s47 [redacted]

Major toxicities

In the repeat-dose toxicity study with IM injections of 50 µg SARS-CoV-2 rS (± 50 µg Matrix-M1), treatment–related findings were limited to inflammation at the injection site with increased subcutaneous (minimal to mild) cellular infiltration, minimal oedema/erythema and myofibre degeneration. At the end of the 21-day recovery period, the inflammation changes partially recovered. Overall, 3 IM injections of SARS-CoV-2 rS (± Matrix-M1) given 7 days apart were locally and systemically well tolerated. Other treatment-related findings included elevated levels of fibrinogen, C–reactive protein and globulin, which lowered during the recovery phase. No effects on spleen and only mild effect on draining lymph nodes (like hyperplasia and inflammation, reported in other studies with Matrix-M1 with or without an antigen) were observed in this study. Mild histiocytic heterophil infiltrate of the right iliac lymph node was observed in only 1 female receiving SARS-CoV-2 rS + Matrix-M1. Serology data demonstrated detection of specific antibodies, with the Matrix-M1 adjuvant significantly enhancing the anti-S IgG response in rabbits.

Other studies including an adjuvant only treatment group demonstrated similar treatment–related findings of acute inflammation (subcutaneous [minimal to mild] cellular infiltration), which fully or partially reversed during the recovery period and elevated serum levels of fibrinogen, C–reactive protein and globulin, which lowered during the recovery phase. s47

[redacted]

Genotoxicity

No genotoxicity studies were conducted for SARS-CoV-2 rS (antigen) or the vaccine formulation. This is in line with relevant guidelines for vaccines.

Matrix-M1 as a novel adjuvant was tested in two non-GLP *in vitro* genotoxicity pilot–studies s47 and two GLP-compliant *in vitro* genotoxicity studies s47 The assays were adequately validated and returned negative results.

No *in vivo* genotoxicity study was provided for the novel adjuvant, Matrix-M1. While the WHO guidelines on the nonclinical evaluation of vaccine adjuvants recommend a standard battery of genotoxicity studies for novel adjuvants that are new chemical entities[2], the Sponsor has not planned to conduct an *in vivo* genotoxicity study as Matrix-M1 adjuvant was non-mutagenic in the GLP *in vitro* genotoxicity studies. The Sponsor indicated that both the EMA and FDA had agreed to the Sponsor's approach on genotoxicity testing of Matrix-M1, and also noted that Quillaja saponins are used as food additives with an acceptable daily intake (ADI) of 1 mg/kg/day (JECFA, for semi-purified extract) or 3 mg/kg (EFSA)[4]. However, there are no data on oral bioavailability of Quillaja saponins, and Quillaja saponins are expected to have very low oral bioavailability based on studies with other saponins. Nonetheless, the saponins in Matrix-M1 are plant-derived and Quillaja saponins have been used as a food additive for decades. Based on all of the above, the absence of *in vivo* genotoxicity studies for Matrix-M1 is considered acceptable.

Carcinogenicity

Carcinogenicity studies were not conducted. This is acceptable based on its duration of use. The novel adjuvant, Matrix-M1 is not expected to be carcinogenic based on the low exposure, duration of exposure, and the negative results in two *in vitro* genotoxicity assays.

Reproductive toxicity

As SARS-CoV-2 rS vaccine is proposed to be used for the active immunisation of individuals from the age of 18 years, there is potential for administration of the vaccine to pregnant women.

A non-GLP pilot study with SARS-CoV-2 rS (10 µg) + Matrix-M1 (20 µg) was conducted first to confirm the immunogenicity of the intended dose and formulation in SD rats. SARS-CoV-2 rS + Matrix M1 was well tolerated and elicited an immune response in rats following 2 IM injections on Days 1 and 15.

A GLP–compliant, combined reproductive and developmental toxicity study with SARS-CoV-2 rS + Matrix-M1, and Matrix-M1 alone in rats showed no test item–related adverse effects on female fertility, and embryofetal and postnatal development. SARS-CoV-2 rS + Matrix M1 elicited an immune response in rats following 4 IM injections. s47 This is acceptable given the absence of effects on male reproductive organs in rats and rabbits receiving up to 4 doses of Matrix-M1-adjuvanted

[4] EFSA Panel on Food Additives and Flavourings. Re-evaluation of Quillaia extract (E999) as a food additive and safety of the proposed extension of use. EFSA J. 2019 Mar 6; 17(3):e05622. doi.org/10.2903/j.efsa.2019.5622.

vaccines or adjuvant alone, and the proposed vaccine would be administered to humans infrequently. Based on the study, this vaccine is not consider to pose a risk for use in pregnant women.

Pregnancy classification

The Sponsor has proposed a pregnancy Category B1. The Pregnancy Category B1 is considered appropriate for this product as the reproductive toxicity study in female rats revealed no adverse effects on embryofetal development or postnatal development of offspring.

Local tolerance

No separate local tolerance studies were submitted. Local tolerance was assessed in the repeat dose toxicity study with SARS-CoV-2 rS (NVX-CoV2373) and studies with Matrix-M1. Local reactions observed in the repeat-dose toxicity studies performed with SARS-CoV-2 rS + Matrix-M1 or Matrix-M1 in rats or rabbits were limited to minimal to mild inflammation at the injection sites, and extending to the sciatic nerve and were fully or partially reversible (see *Repeat-dose toxicity* above).

Adjuvant – Matrix-M1

Matrix-M1 adjuvant is derived from fractionated *Quillaja saponins* plus phosphatidylcholine, and cholesterol formulated into ~40 nm cage-like structures. Matrix-M1 is a novel adjuvant, and nonclinical toxicity study requirements for a new chemical entity (NCE) are applicable.

GLP–compliant repeat-dose toxicology studies in rats and rabbits with the Matrix-M1 adjuvant were submitted, along with a combined reproductive and developmental toxicity study (with a Matrix-M1 only treatment group) and two *in vitro* genotoxicity studies. Toxicological effects of Matrix–M1 in the submitted studies have been evaluated and discussed in the relevant sections above. Safety of the novel adjuvant, Matrix-M1 has been adequately assessed in animal studies. The planned tissue distribution study will provide further information on mechanisms of action and target tissues of potential toxicity.

Paediatric use

SARS-CoV-2 rS (NVX-CoV2373) is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for SASR-CoV-2 rS with Matrix-M1 adjuvant detailed in the Sponsor's draft European Union Risk Management Plan (Part II: Module SII) are in general concordance with those of the Nonclinical Evaluator.

PRODUCT INFORMATION

The following comments refer to the draft Product Information document (1.3.1.2 NUVAXOVID product information v0.4 - tracked 29 Dec 21; TRIM reference D21-3479674). Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

With no relevant nonclinical studies available, the proposed statement is considered to be acceptable from a nonclinical perspective.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

It should be mentioned that the reproductive and developmental toxicity study in rats did not evaluate effects on male fertility. Additionally, the relative exposure for Matrix-M1 adjuvant should be corrected. The preferred Australian spelling of *fetus* should be used (the additional *'o'* having no etymological basis[5]). The following text is recommended:

> "Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
>
> A developmental and reproductive toxicity study was performed in female rats administered four intramuscular doses (2 prior to mating; 2 during gestation) of 5 micrograms SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 micrograms on a weight-adjusted basis) with 10 micrograms Matrix-M adjuvant (approximately s47 -fold excess relative to the human dose of 50 micrograms on a s47 -adjusted basis). No vaccine-related adverse effects on s47 fertility, pregnancy/lactation, or development of the s47 and offspring through post-natal Day 21 were observed. s47

Use in pregnancy

The sponsor proposes Pregnancy Category B1 and the following statement:

> "Proposed pregnancy category – B1.
>
> There is limited experience with use of NUVAXOVID in pregnant women.
>
> Animal studies did not show vaccine related adverse effects on embryofetal development (see Effects on fertility).
>
> Administration of NUVAXOVID in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus."

The proposed Pregnancy Category B1 is considered appropriate for this product as no embryofetal effects have been noted in a combined reproductive and development study in rats. The preferred Australian spelling of fetus should be used. The statement regarding the proposed pregnancy

[5] Macquarie Dictionary usage note: The etymology of this word is from a Latin form *fetus*. The spelling *foetus*, probably based on false analogy with words such as *oedema* and *oestrogen*, was widely used, although health authorities increasingly recommend the spellings *fetus* and *fetal*.

category should be removed since it is already noted in the heading. The following changes are recommended:

s47 [redacted]

There is limited experience with use of NUVAXOVID in pregnant women.

s47 [redacted] did not show vaccine related adverse effects on embryofetal development (see Effects on fertility).

Administration of NUVAXOVID in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and s47 [redacted]

Use in lactation

The proposed text is acceptable with a minor editorial change. The preferred Australian spelling of fetus should be used. Thus:

"It is unknown whether NUVAXOVID is excreted in human milk."

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Statements on the mechanism of action are supported by nonclinical data. Minor editorial changes are suggested. Thus:

"NUVAXOVID is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The 2 vaccine components elicit B- and T-cell immune responses to the S protein, including s47 [redacted], which protect against COVID-19."

5.3 PRECLINICAL SAFETY DATA

Statements regarding general and reproductive toxicity should be deleted from this section. Thus:

s47 [redacted]

Genotoxicity

Information on the genotoxicity assays conducted should be provided and "*In vitro*" should be italicised. Thus:

s47 [redacted]

were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic."

Carcinogenicity

The proposed statement noting the absence of carcinogenicity studies is considered acceptable.

"Carcinogenicity studies were not performed. The components of the vaccine are not expected to have carcinogenic potential."

MAIN BODY OF REPORT

1. INTRODUCTION

1.1. BACKGROUND

Biocelect Pty Ltd has applied for provisional registration of a new COVID-19 vaccine (also known as NVX-CoV2373 or Novavax COVID-19 Vaccine) (NUVAXOVID®). The vaccine consists of a recombinant (r) spike (S) protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as SARS-CoV-2 rS, as the antigen and Matrix-M1 as the adjuvant. It is indicated for the active immunisation for the prevention of mild, moderate, and severe disease caused by SARS-CoV-2 in adults ≥18 years of age. The proposed dosing regimen is 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) given on Days 0 and 21 intramuscularly (IM).

1.2. RELATED VACCINES

SARS-CoV-2 rS (NVX-CoV2373) vaccine is the first SARS-CoV-2 recombinant spike protein adjuvanted vaccine to be proposed for registration in Australia. There are currently two other vaccines registered for COVID-19, ChAdOx1-S COVID-19 Vaccine (COVID-19 VACCINE ASTRAZENECA®) and BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY™).

1.3. RECOMBINANT SARS-COV-2 SPIKE PROTEIN CONSTRUCT

SARS-CoV-2 recombinant (r) spike (S) protein (SARS-CoV-2 rS) vaccine is constructed from the full-length, wild-type SARS-CoV-2 spike protein gene sequence (GenBank MN908947; nucleotides 21563–25384). It was codon optimised to improve expression in *Spodoptera frugiperda* (Sf9) insect cells. The construct was modified at the S1/S2 cleavage site (RRAR to QQAQ [3Q]; see below) to make it protease resistant. Two proline substitutions were inserted in the S2 fusion machinery within the heptad repeat 1 domain (HR1; at residues K986 and V987 [2P]) to enhance S2 stability in a prefusion conformation (Bangaru *et al.,* 2020; Wrapp *et al.,* 2020). The double mutant 3Q-2P SARS-CoV-2 rS transgene was cloned into the baculovirus[6] transfer vector. Recombinant baculovirus constructs were then transfected into Sf9 insect cells.

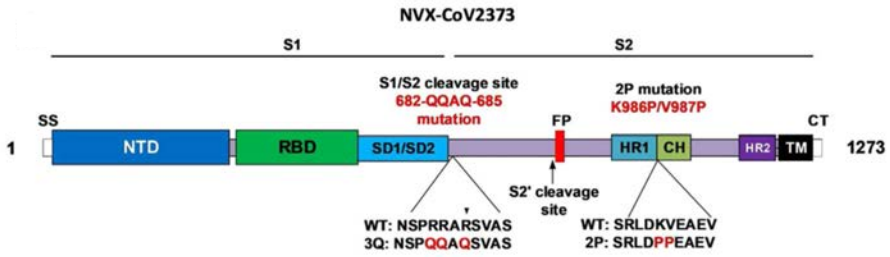

Figure 1.1. Full-length optimised spike protein construct (reproduced from Tian *et al.,* 2021)

[6] an insect enveloped virus; highly infectious to cultured insect cells and non-pathogenic to humans

1.4. SARS-CoV-2 rS VACCINE ADJUVANT

Isolated and purified SARS-CoV-2 rS protein trimers were adjuvanted with the saponin-based Matrix-M1 adjuvant. The Sponsor indicated (TRIM reference D20-3630324) that the adjuvant "*is derived from fractionated Quillaja saponins, phosphotidyl choline, and cholesterol formulated into ~40 nm cage-like structures. Quillaja saponins are extracted from the bark of the tree Quillaja saponaria Molina, in a multi-step process before being mixed with cholesterol and phospholipids using a proprietary method to create the Matrix particles. Matrix-M1 is formulated in phosphate buffered saline (PBS) to create the bulk adjuvant.*"

1.5. PRODUCT FORMULATION

SARS-CoV-2 rS (NVX-CoV2373) supplied as a preservative free liquid formulation for IM administration. It is available as vials containing 10 doses of 0.5 mL/dose of vaccine. The vaccine contains Matrix-M1 as adjuvant, and SARS-CoV-2 rS antigen (laboratory code BV2373); produced by recombinant technology from Sf9 cells (see Section 1.3). Quantities of antigens, adjuvant and excipients are outlined below in Table 1.1~~Table 1.1~~.

Table 1.1. Product formulation

Ingredient	Function		s47 [redacted]	
SARS-CoV-2 rS (NVX-CoV2373)	Active ingredient			
Matrix-M1*	Adjuvant			
Disodium hydrogen phosphate heptahydrate	NA			
Sodium dihydrogen phosphate monohydrate	NA			
Sodium chloride	NA			
Polysorbate 80	Stabilizer			
Sodium hydroxide	pH			
Hydrochloric acid	pH			
Water for injection	Solvent			

* = Matrix-A and Matrix-C components are mixed to form Matrix-M1 adjuvant, just prior to mixing with DS. Matrix-M1 is a novel excipient
NA = not available

1.6. MATRIX-M1 ADJUVANT

Martix-M1 adjuvant is a novel excipient, derived from fractionated Quillaja saponins, phosphatidylcholine, and cholesterol formulated into s47 [redacted] nm diameter cage-like structures (TRIM reference D20-3630324).

1.6.1. Saponins structure and Matrix-M1 adjuvant formulation

In its email to TGA names dated 14 January 2021 (TRIM reference D21-2056500) the Sponsor provided the following information: "*SARS-CoV-2 rS vaccine includes an adjuvant (Matrix-M1) which is manufactured using fractionated Quillaja saponins derived from the tree Quillaja saponaria Molina. The Fraction-A and Fraction-C saponins are produced from saponin raw material… The saponin fractions consist of the structurally related saponins* s47 [redacted]

s47 [redacted]

As indicated above, Fraction-A and Fraction-C "*consist of a number of structurally related saponin components*". The identification and characterisation of the saponin residues in Fraction-A and Fraction-C was performed by LC/ESI-MS/MS. The study showed that *"the fractions contain a few major saponins and a number of minor saponins.* s47 [redacted]

s47 [redacted]

The Sponsor also indicated that *"the purified Fraction A and Fraction C are then formulated to Matrix-A and Matrix-C which are identified by individual company codes"* 10-100-402 and 10-010-202, respectively (AAN application, TRIM reference D21-2056500).

Matrix-A and Matrix-C are nanoparticles made of purified saponin fractions, cholesterol, and phospholipid (TRIM references D20-3630324 & D20-3665265). The Sponsor specified that the drug product (DP) is formulated by mixing Matrix-A (85%) and Matrix-C (15%) into Matrix-M1 and adding the antigen (TRIM reference D20-3665265). s47 [redacted]; TRIM reference D20-3630324).

There is no information on the amount of cholesterol and phospholipid in Matrix-M1. This will be included after the submission of Module 3 data. Since both cholesterol and phospholipid are common excipients in parenteral formulations, they are not considered to be of safety concern.

1.6.2. Saponins structure-activity relationship

According to the published literature, saponin-based adjuvants have been studied for use in the development of new vaccines (Didierlaurent *et al.,* 2014; Wilson *et al.,* 2012). They have been shown to activate cytokine production (IFNs and ILs). Adjuvanticity of saponins is due to the presence of different residues to the main triterpenoid (C30) structure (see Figure 1.2~~Figure 1.2~~). Several published papers have proven a direct relationship between the saponins structure and activity (for review see Sharma *et al.,* 2020; Rajput *et al.,* 2007). The presence of

- aldehyde group plays a "*role in maintaining the integrity and strength of Th1 response. Axial aldehyde shifts the immune system toward the stimulation of humoral immune responses, whereas equatorial aldehyde produces cell-mediated immune responses.*" (Sharma *et al.,* 2020)
- acyl groups enhance the activation of cytotoxic T lymphocytes (CTL). "*Deacylation of saponins… shows reduced antibody production and Th1 response compared to the acylated saponin, suggesting that the acyl residues are important for the activation of CTL-mediated immune response.*" (Sharma *et al.,* 2020)
- sugar chains are involved in the initiation of the immune response and also have an haemolytic effect (Sharma *et al.,* 2020). It has been demonstrated that "*the balance between these sapogenin [aglycone] (hydrophobic) and sugar chain (hydrophilic) properties is important for maintaining the adjuvanticity of saponins.*"

Saponin molecules can cause haemolysis of red blood cells; which is presumably due to their affinity for cell membranes components such as cholesterol and phospholipids (for review see Lorent *et al.,* 2014). In their review, Sharma *et al.* (2020) indicated that the *"hemolytic activity of the saponin molecules is mainly due to the presence of saccharide side chain and the acyl residues in the aglycone*". However, the haemolytic activity of saponins does not appear to be related with their adjuvanticity (Sharma *et al.,* 2020; Rajput *et al.,* 2007). Rönnberg *et al.* (1995) demonstrated that complexing *Quillaja saponaria* Molina saponin with cholesterol and phospholipid molecules to form a cage-like structure adjuvant (ISCOM) reduced the haemolytic activity associated with saponins. Therefore, the haemolytic activity of saponin contained in the proposed SARS-CoV-2 rS vaccine is not considered to be a potential safety concern when complexed with cholesterol and phospholipids.

However, based on the above it is considered that the different saponins present in Matrix-M1 adjuvant can affect the DP pharmacokinetics, immunogenicity and safety. The data provided in Module 4 is not sufficient to accurately establish the safety and/or efficacy of Matrix-M1 adjuvant in the DP. The Sponsor was requested to address items 1–4 below. A response to the S31 request (see below) was received on 31st May 2021.

1. Does the Sponsor have a strategy in place to monitor the relative amount of each saponin component contained in Fraction-A/Matrix-A, Fraction-C/Matrix-C or Matrix M1?

s47

The purity of Fraction-A and Fraction-C saponins is tested by HPLC and batch release testing for three batches of Fraction-A and Fraction-C demonstrated comparability.

It should be noted that the initial characterisation of saponin fractions demonstrated that Fraction-A has poor to no adjuvanticity and its haemolytic potential is low; while Fraction-C has potent adjuvant activity and medium haemolytic potential. Both fractions were shown to contain saponins with good matrix-forming ability (see Table 4-1).

s47

2. Please provide composition details of each Matrix-M1 batch (including the concentration of each saponin component) used in nonclinical and clinical studies.

The Sponsor indicated that the saponin content in Matrix-A and Matrix-C is characterised at the Fraction-A and Fraction-C level. "*The saponin components in the Fraction-A and Fraction-C materials are governed by the fractionation process… The target composition of Matrix-A and Matrix-C in Matrix-M1 is 85:15 (w:w* [ratio 5.67]*) as measured by the Fraction-A and Fraction-C concentrations, respectively.*"

s47

3. Please provide information on any differences in the manufacture of Fraction-A/Matrix-A, Fraction-C/Matrix-C and Matrix M1 batches used in the nonclinical studies and clinical studies (including batches for marketing).

The Sponsor indicated that "*There are no differences between the manufacture of Fraction-A/Matrix-A, Fraction-C/Matrix-C, and Matrix-M1 batches used in the nonclinical studies and clinical studies in relation to formulation or composition, nor is there any plan to change the formulation or composition with respect to batches being manufactured for marketing.*"

4. Please comment on the impact of saponin components variations in Matrix-M1 on the safety and efficacy of Matrix-M1 and the vaccine.

The Sponsor pointed out that several batches of Matrix-M1 were used in *in vivo* primary pharmacology studies and repeat-dose toxicity studies. All tested batches produced strong adjuvant-related immune responses. The Sponsor indicated that no adjuvant-related changes in safety profile was observed in these studies and that the adjuvant was overall well tolerated. Similarly, Matrix-M1 based vaccines "*are generally well tolerated and have an acceptable safety profile*" in clinical studies. The Sponsor considers that because the "*safety (reactogenicity) and immune responses have been consistent across clinical trials … which led to demonstration of vaccine efficacy of 89.7% in a Phase 3 trial … Thus, the safety and efficacy obtained in nonclinical and clinical studies for SARS-CoV-2 rS with Matrix-M1 adjuvant is expected to be representative of the minor variations in saponin components (within specifications) that will be used in the commercial setting and no impact on the safety or efficacy have been observed within this variation.*"

Conclusion:

The Nonclinical Evaluator notes that although the "*purity of the fractions has been increased*", the "*diversity and content of the core fractions*" has been maintained. Based on the Sponsor's S31 response, it appears that the exact component content of Fraction-A and Fraction-C saponins will not be determined. Initial characterisation of fractions of saponins showed that Fraction-A has poor to no adjuvanticity with a low haemolytic potential, while Fraction-C has potent adjuvant activity and medium haemolytic potential. The Nonclinical evaluator considers that the variation in the amount of Matrix-C present in Matrix-M1 is more likely to impact the safety and efficacy of the adjuvanted vaccine. s47 [redacted] The variability in Matrix-C concentration in the DP is considered marginal and major changes in Matrix-M1 safety and efficacy are not expected.

1.7. BATCHES USED IN MODULE 4 STUDIES

The tables below list the antigen (SARS-CoV-2 rS – BV2373) and Matrix-M1 adjuvant batches (Table 1.4 and Table 1.5~~Table 1.5~~) as well as Matrix-M1 formulation (Table 1.6) used in the nonclinical studies.

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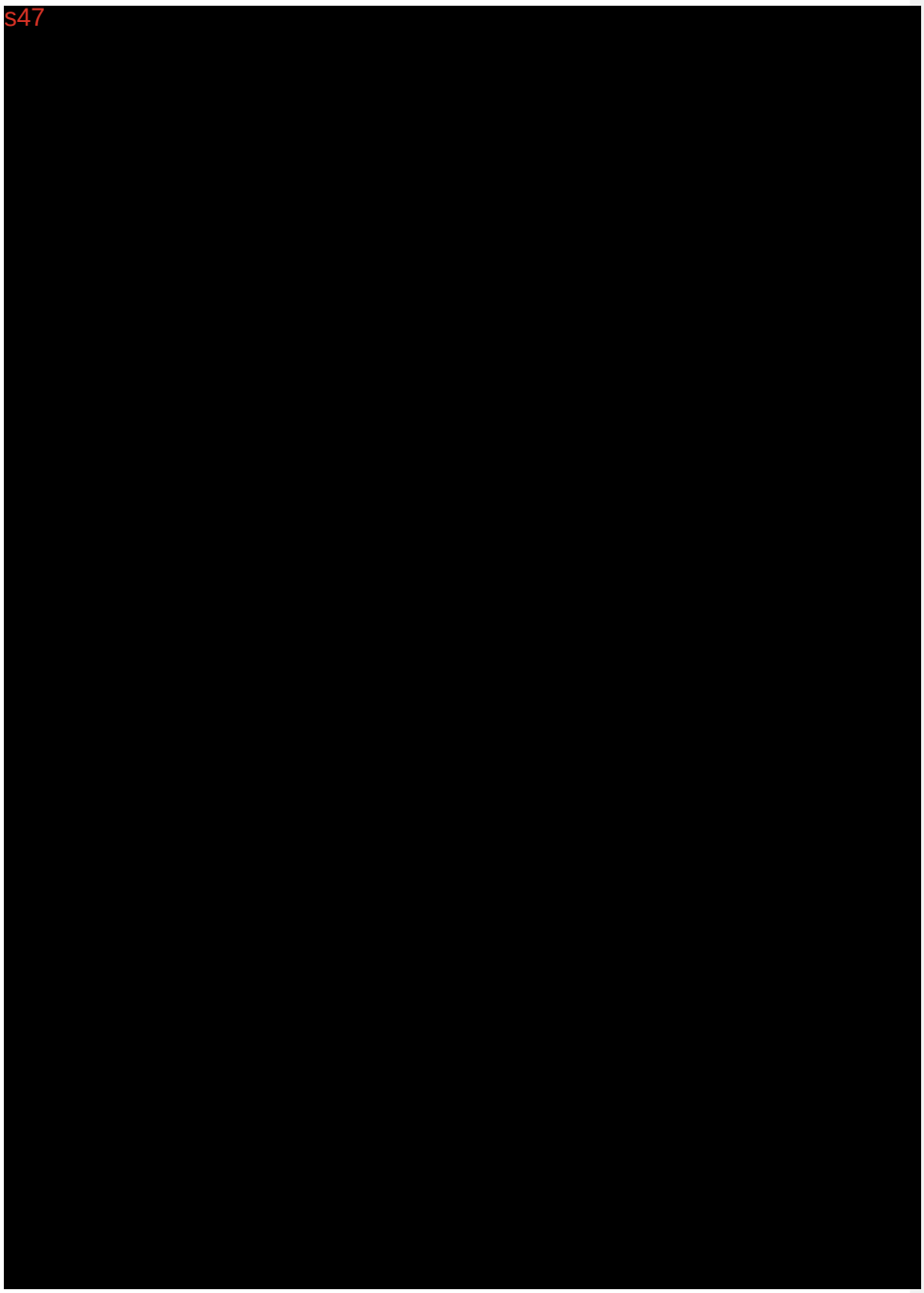

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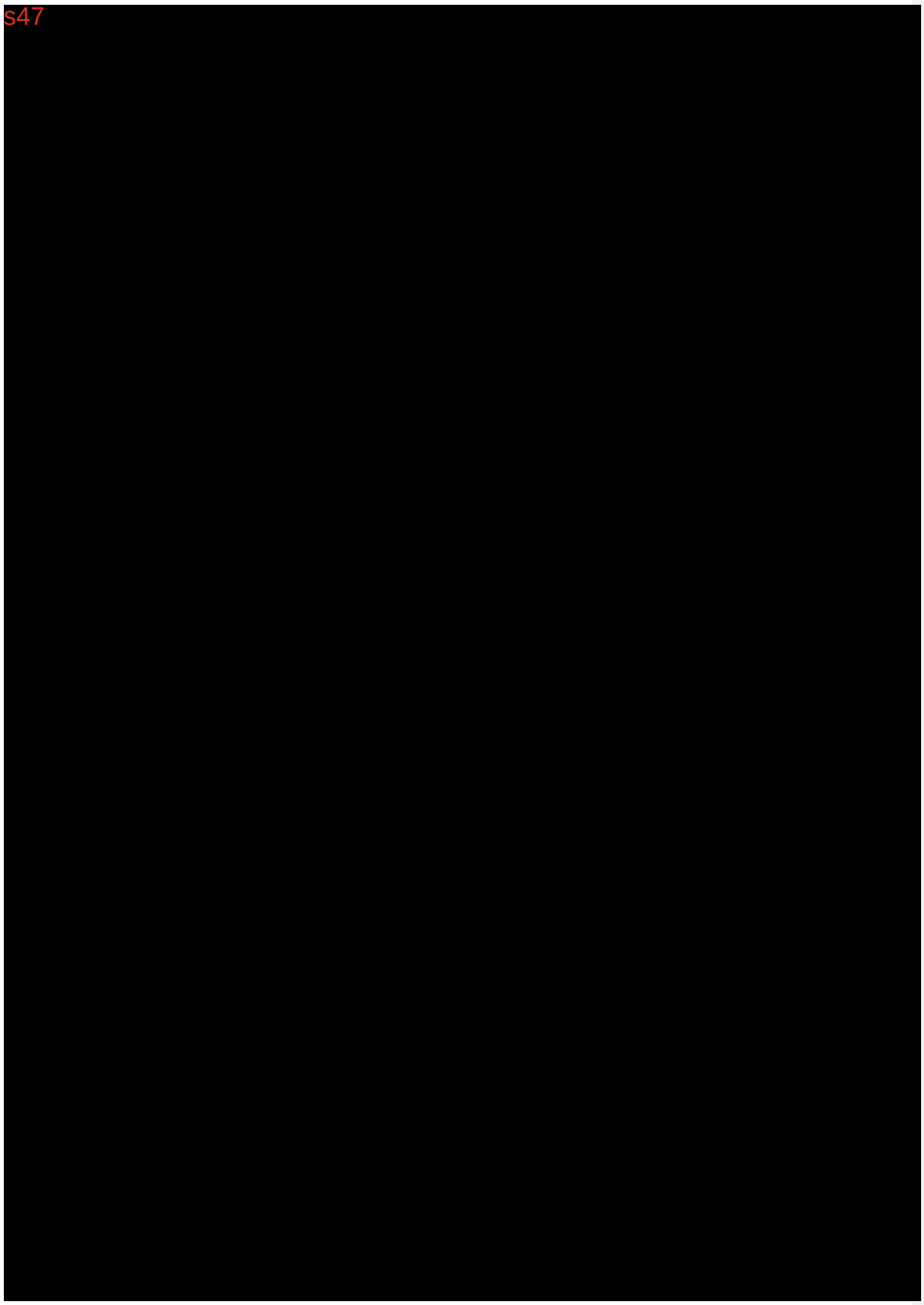

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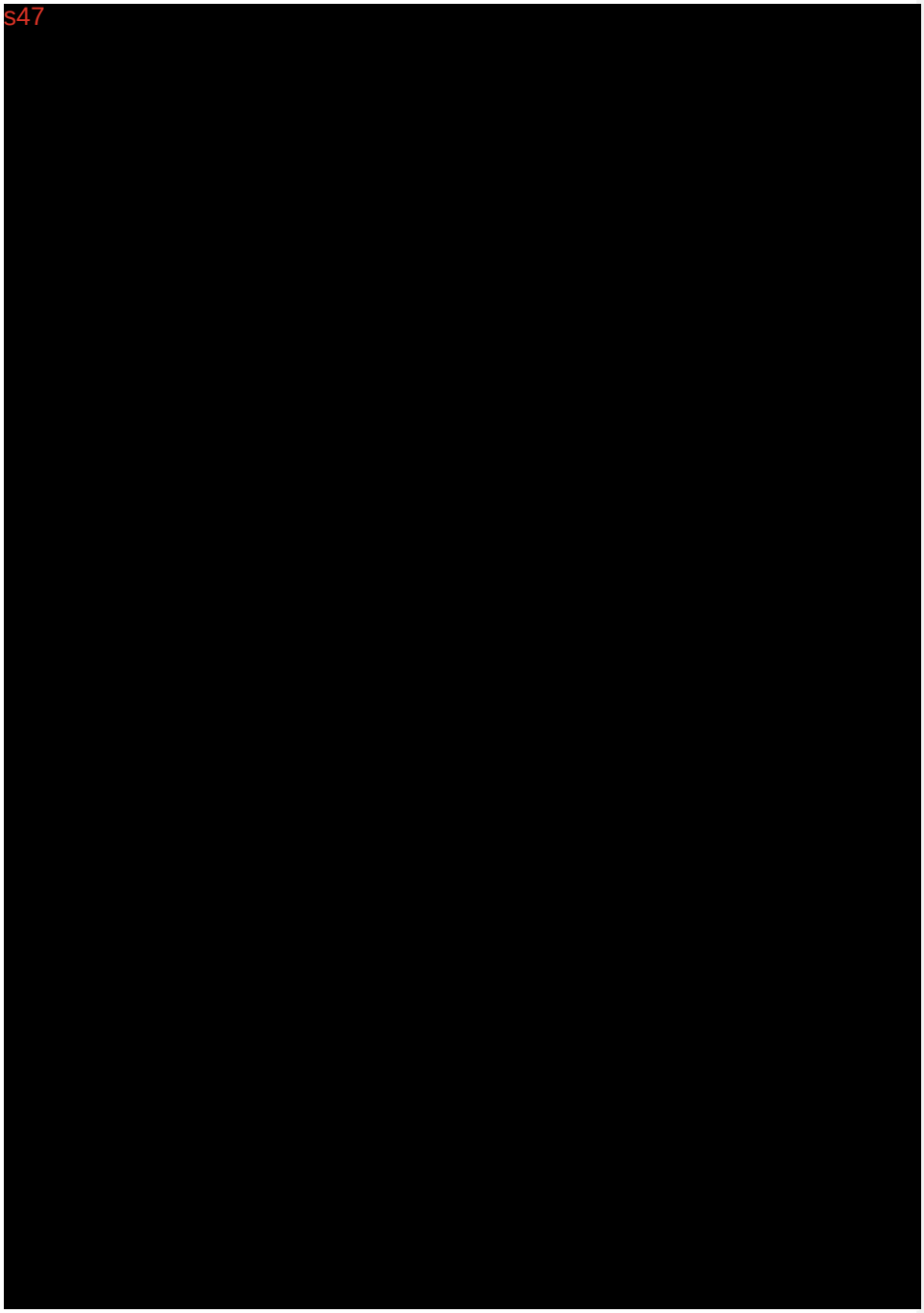

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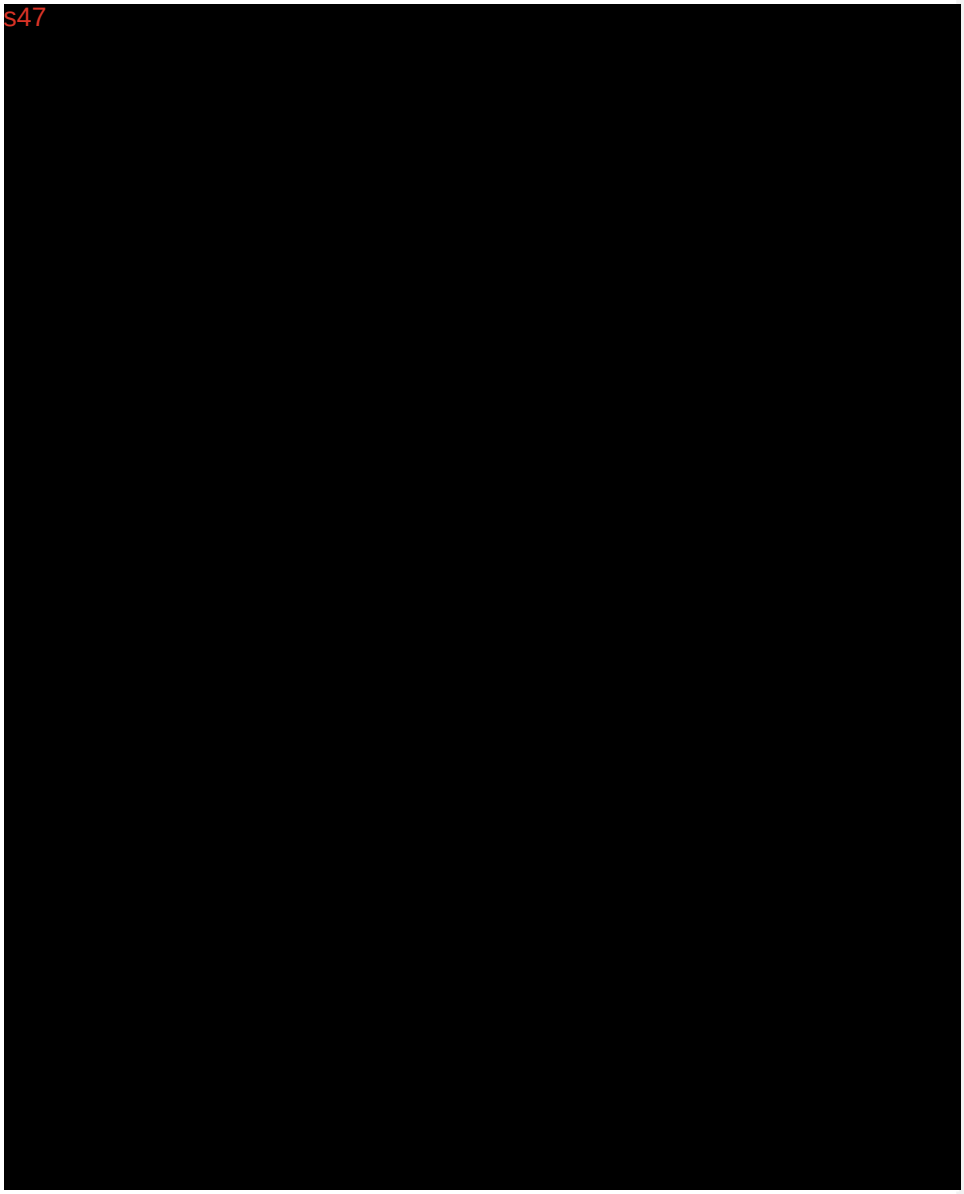

The nonclinical studies were conducted with the drug substance produced at a small-scale (10 L); which according to the Sponsor s47

However, it appears that the manufacturing process as well as manufacturing sites have changed since completion of the nonclinical studies. The DS/DP used in the nonclinical studies might not be comparable with the product to be marketed in Australia. The Sponsor has been requested to comment on the following questions:

1. Please provide information on differences between the batches (including antigen, final formulation and adjuvant) used in nonclinical studies and commercial batches to be marketed in Australia.
2. Are there nonclinical studies assessing the comparability of the nonclinical and commercial batches? If not, please provide justifications for not conducting nonclinical comparability studies between the manufacturing sites, including a discussion on the impact of any differences on efficacy and safety of the vaccine.

Sponsor's response to the above questions (received on 16 December 2021):

The response provided by the Sponsor (in a non-eCTD format) is not considered to adequately address the questions above.

The Sponsor indicated that there was no difference in antigen, final formulation, or adjuvant in the drug product batches used in non-clinical studies conducted in Non-Human Primates (2020-08-702-094, 2020-11-702-099, and 702-111) compared to the batches used in clinical studies or the batches proposed for commercial use in GMP (Good Manufacturing Practice) facilities. The Sponsor noted that the drug substance produced at s47 were shown to be comparable based on Module 3 data, and also additional mouse immunogenicity studies comparing nonclinical and clinical batches of drug substance and drug product. However, 6 immunogenicity studies mentioned in the response could not be located in Module 4 of the dossier. Therefore, additional 3 questions were communicated to the Sponsor (see below).

s47

The Sponsor's response to Questions 1–3 was received on 24th December 2021.

1. Several studies mentioned in the Sponsor's S31 response cannot be located in Module 4. The Sponsor is requested to provide these studies: mouse immunogenicity studies (2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, 2021-22-702-132 and 702-157) and nonclinical study in non-human primate (702-111).

Sponsor's response to Question 1:

The Sponsor submitted the reports for studies 2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, and 2021-22-702-132 noted in the above response and indicated that "*Studies 702-157 and 702-111 are in the reporting phase and reports will be available in Q2 2022*."

Nonclinical assessment of the Sponsor's response to Question 1:

Studies 2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, and 2021-22-702-132 have been evaluated in the present report (see Section 2.2.1).

2. Can the Sponsor provide a comparison between the manufacturing processes used to produce the batches tested in the nonclinical studies and the manufacturing processes used to produce the commercial batch(es) that will be released in Australia; in terms of DS (antigen, Matrix-M1) and DP (vaccine)?
    a. In what are they similar?
    b. In what do they differ?
    c. How can these differences affect safety and efficacy?

Sponsor's response to Question 2:

The Sponsor indicated that the manufacturing process for producing the purified antigen "*in the Novavax Discovery laboratories for use in nonclinical studies was substantially similar to the process used at SIIPL* [Serum Institute of India Pvt. Ltd.] *for the commercial lots*". Table 1.7 lists the similarities and differences in DS and DP manufacturing processes for the batches used in the nonclinical studies and the commercial batch(es) for release in Australia.

Antigen:
The Sponsor indicated that the differences in the antigen manufacturing process were represented in one clinical batch (FDBU 2000 L). The Sponsor specified that efficacy was demonstrated in the clinical studies conducted with this batch and no safety concerns were identified.

Matrix-M1:
The Sponsor stated that "*the Matrix-M1 batches used in the nonclinical studies… were mixed from Matrix-A and Matrix-C adjuvant components manufactured at the Novavax AB site in Uppsala, Sweden (NVX-AB) at a* s47 [redacted]
The Sponsor indicated that "*A comprehensive analytical comparability package demonstrated comparability across Matrix-A and Matrix-C batches manufactured at the* s47 [redacted] *scales*".

Vaccine:
The Sponsor notified that "*BV2373 antigen lot Discovery 16Apr20 (produced by Novavax, Inc. at laboratory scale)*" and "*The adjuvant lots (M1-108 and M1-111…)…* s47 [redacted] *by Novavax AB"* used in two NHP nonclinical studies (Study 702-094 in cynomolgus macaques and Study 702-099 in rhesus macaques) "*were also used in clinical studies*". "*The DP processes used for both the non-clinical lots and the commercial batches involve the use of DS and Matrix – formulated with a buffer of 300mM Sodium Chloride, 25mM Sodium Phosphate, and 0.01% PS80, at a pH of 7.2. In addition to the scale difference noted above, other differences in the DP process include:*

- *Use of pre-formulated Matrix-M1 for non-clinical lots and the use of separate Matrix A and Matrix C fractions for commercial lots.*
- *PS80: Croda Highly Purified and/or Super Refined grade was used for non-clinical lots and NOF will be used for commercial lots.*

None of these changes are considered to be significant and will not affect safety or efficacy."

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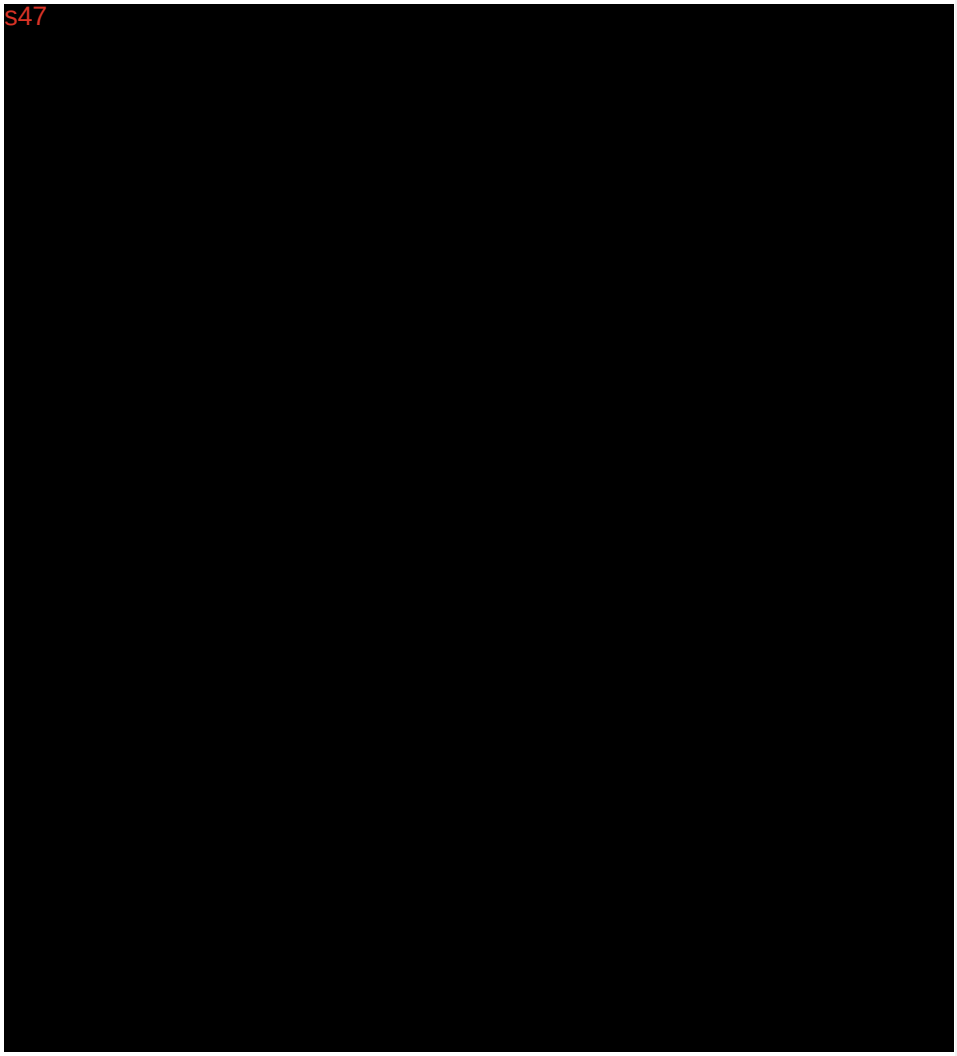
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s47 [redacted]

Nonclinical assessment of the Sponsor's response to Question 2:

Based on the data provided by the Sponsor the manufacturing processes used to produce the antigen (rS protein), adjuvant (Matrix-M1) and vaccine appear to have substantially changed throughout the development of the DS and DP. The quality (Module 3) data for the DS and DP are currently under evaluation. s47 [redacted]

s47 [redacted]

The Nonclinical Evaluator notes that Matrix-M1 batch M1-108 has been used in several clinical studies. However, references to Matrix-M1 batch M1-111 could not be located in Module 2.5 (Table 2.5-2).

3. Have the commercial batch(es) that will be released in Australia been tested in nonclinical studies?
    a. If so, indicate in which studies and, if not already submitted to TGA, please provide the studies.
    b. If not, justify why nonclinical comparative studies have not been conducted.

Sponsor's response to Question 3:

The Sponsor stated that considering "*the robustness of the in vitro analytical assays and ethics concerns*", no nonclinical *in vivo* studies were conducted with the commercial batches. Instead, "*comparability testing of SIIPL lots has been performed using 19 analytical assays and these lots have been shown to be comparable to lots used in Phase 3 clinical studies*".

Nonclinical assessment of the Sponsor's response to Question 3:

The accuracy and reliability of the analytical assays mentioned in the Sponsor's response to Question 3 and therefore the comparability between SIIPL, clinical and nonclinical batches solely depend on the evaluation of the quality studies submitted (assuming the comparability studies/analytical assays have been submitted in Module 3).

1.8. OVERSEAS REGULATORY STATUS

A similar application has been made in the EU, UK, Canada and New Zealand (all between January and February 2021; EU application approved in December 2021).

1.9. SCOPE OF NONCLINICAL DATA

Module 4 comprised nonclinical studies with the clinical formulation. As a rolling submission, interim nonclinical data have been provided. Finalised study reports are expected to be submitted later. Up to 28 April 2021, most nonclinical data have been provided and reviewed in this evaluation report, with only two long term immunogenicity studies and one tissue distribution study, which are ongoing, to be provided in future submissions.

[7] Albanese A., Tang P.S. and Chan W.C. (2012) The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu. Rev. Biomed. Eng. 14: 1–16.

Dobrovolskaia M.A., Aggarwal P., Hall J.B. and McNeil S.E. (2008) Preclinical studies to understand nanoparticle interaction with the immune system and its potential effects on nanoparticle biodistribution. Mol. Pharm. 5: 487–495.

Niikura K., Matsunaga T., Suzuki T., Kobayashi S., Yamaguchi H., Orba Y. *et al.* (2013) Gold nanoparticles as a vaccine platform: influence of size and shape on immunological responses in vitro and in vivo. *ACS Nano* **7:** 3926–3938.

Sun Y.N., Wang C.D., Zhang X.M., Ren L. and Tian X.H. (2011) Shape dependence of gold nanoparticles on in vivo acute toxicological effects and biodistribution. J. Nanosci. Nanotechnol. 11: 1210–1216.

2. PRIMARY PHARMACOLOGY

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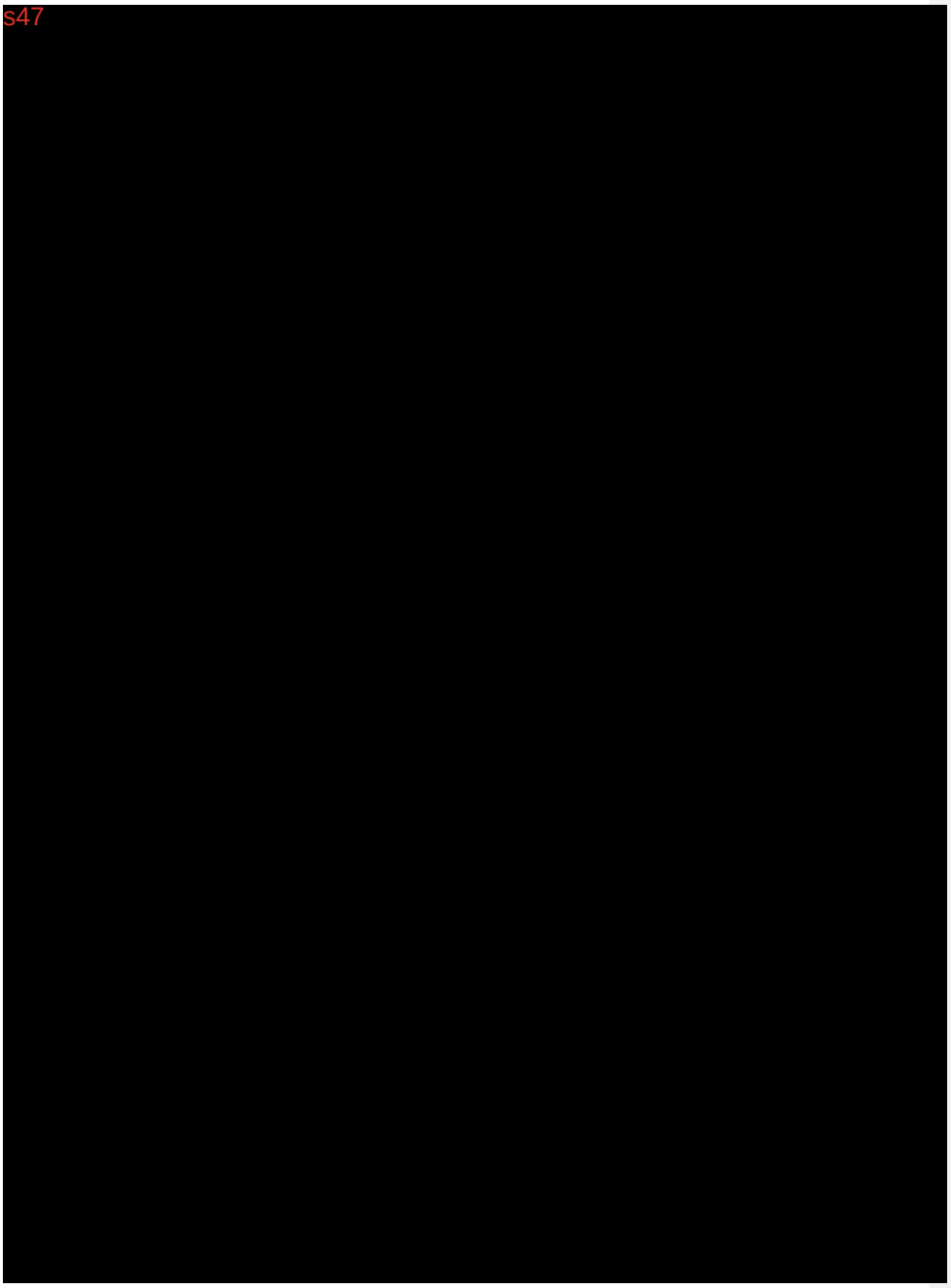

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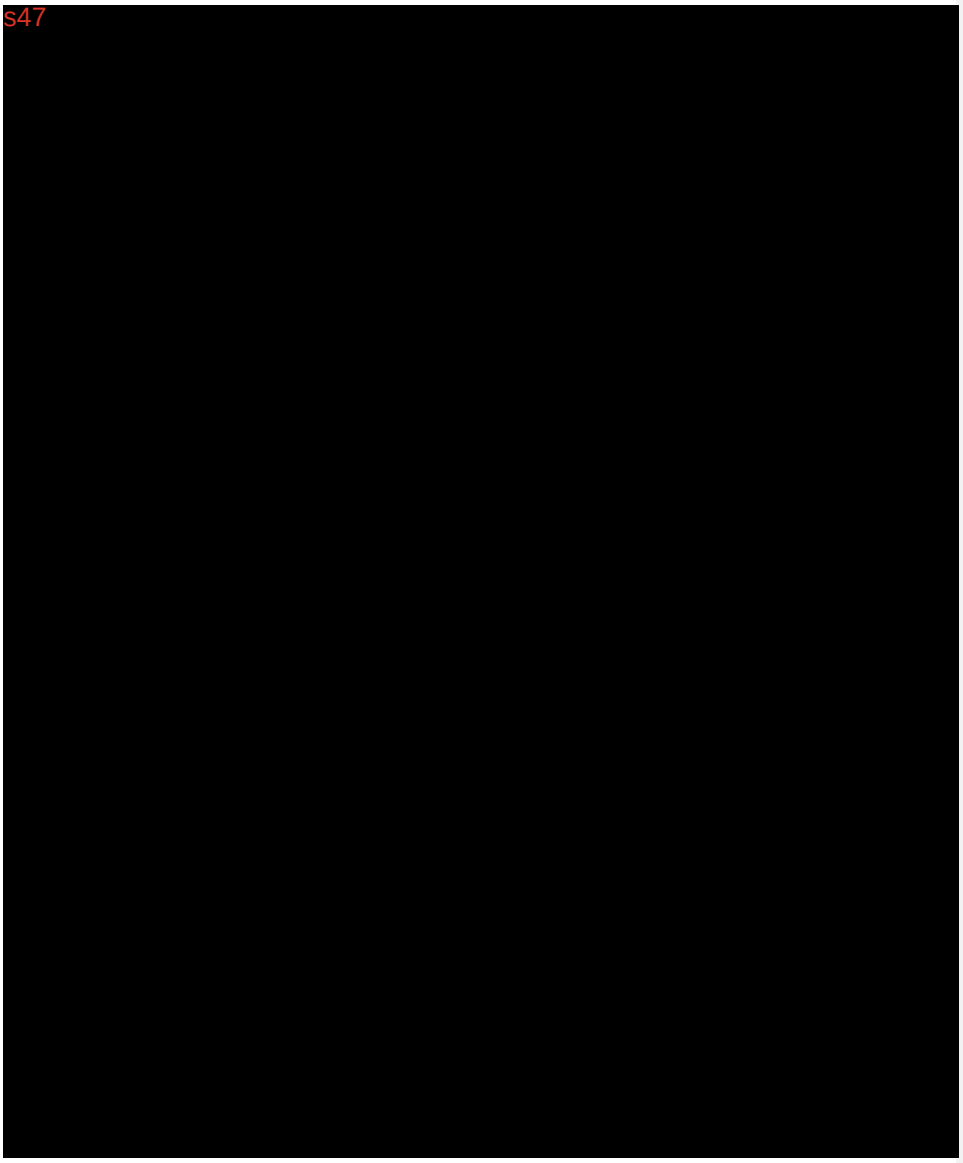

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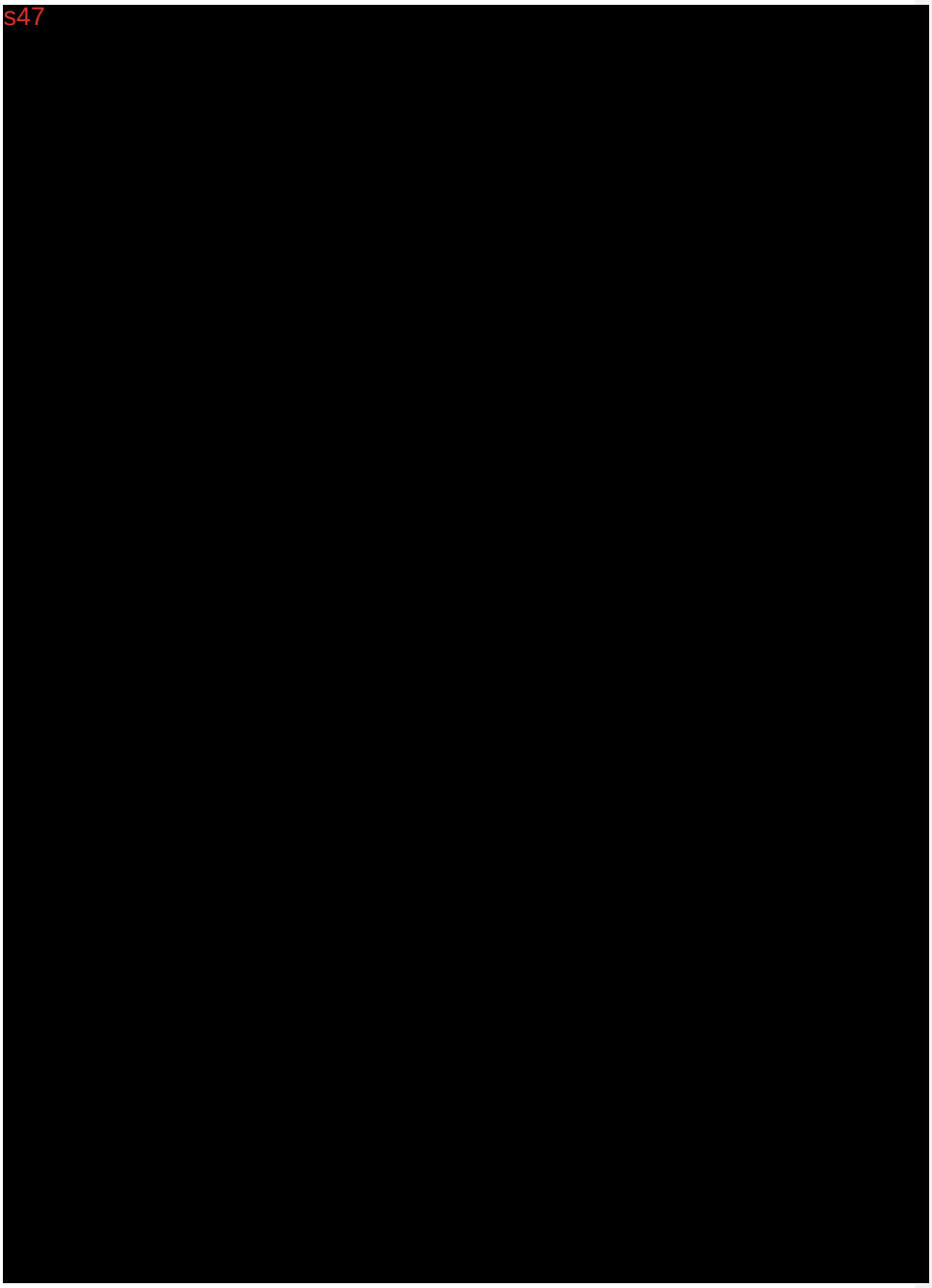

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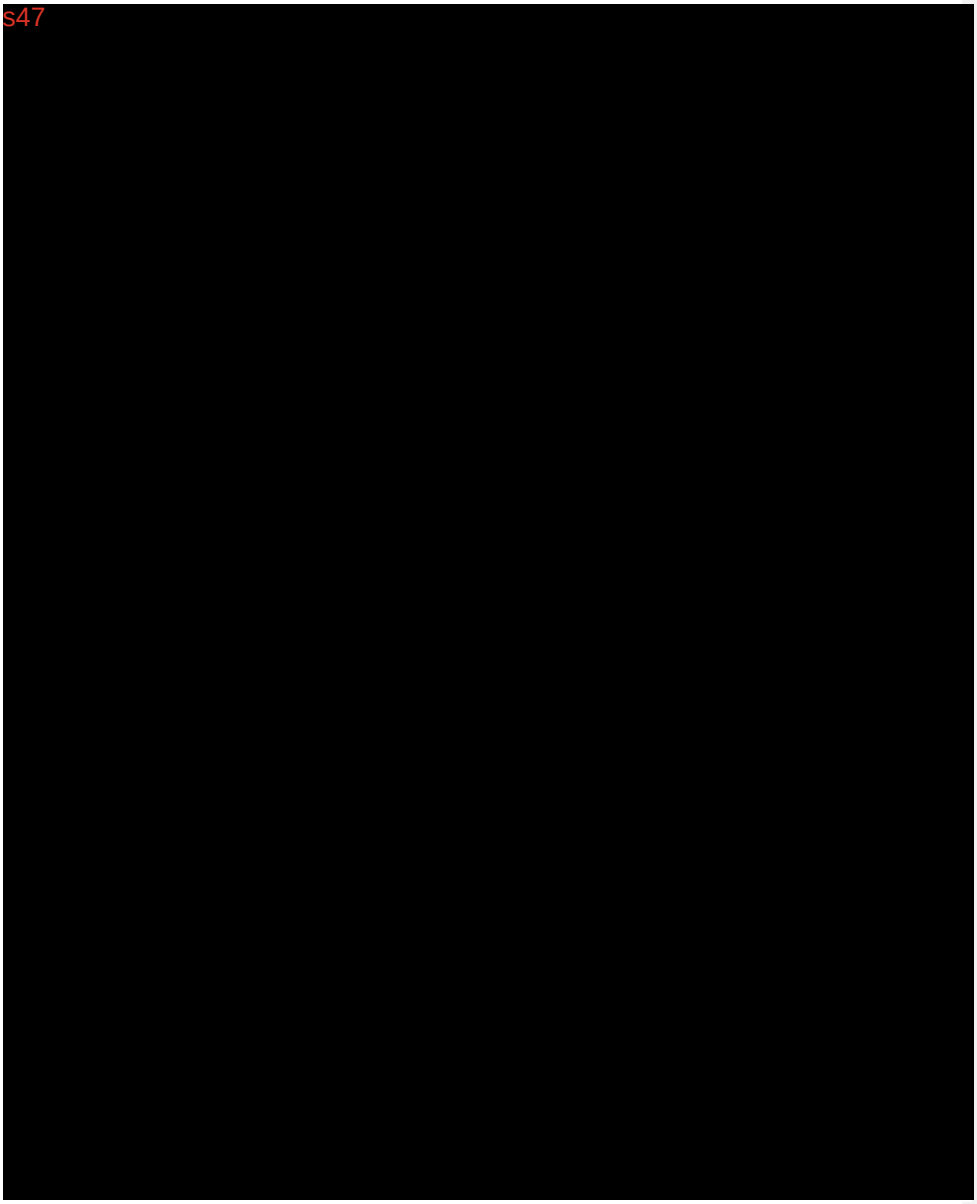

2.1. MATRIX-M1 MECHANISM OF ACTION

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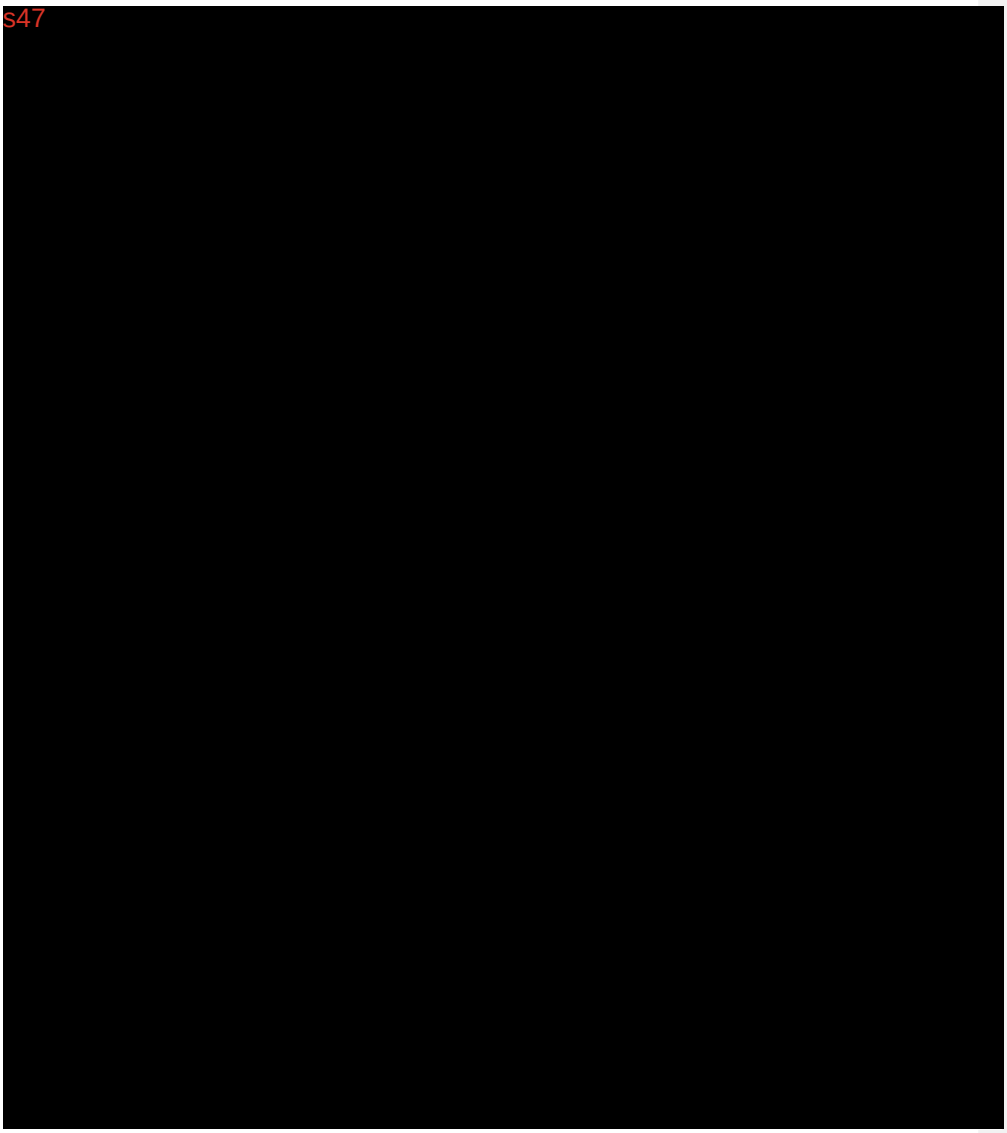

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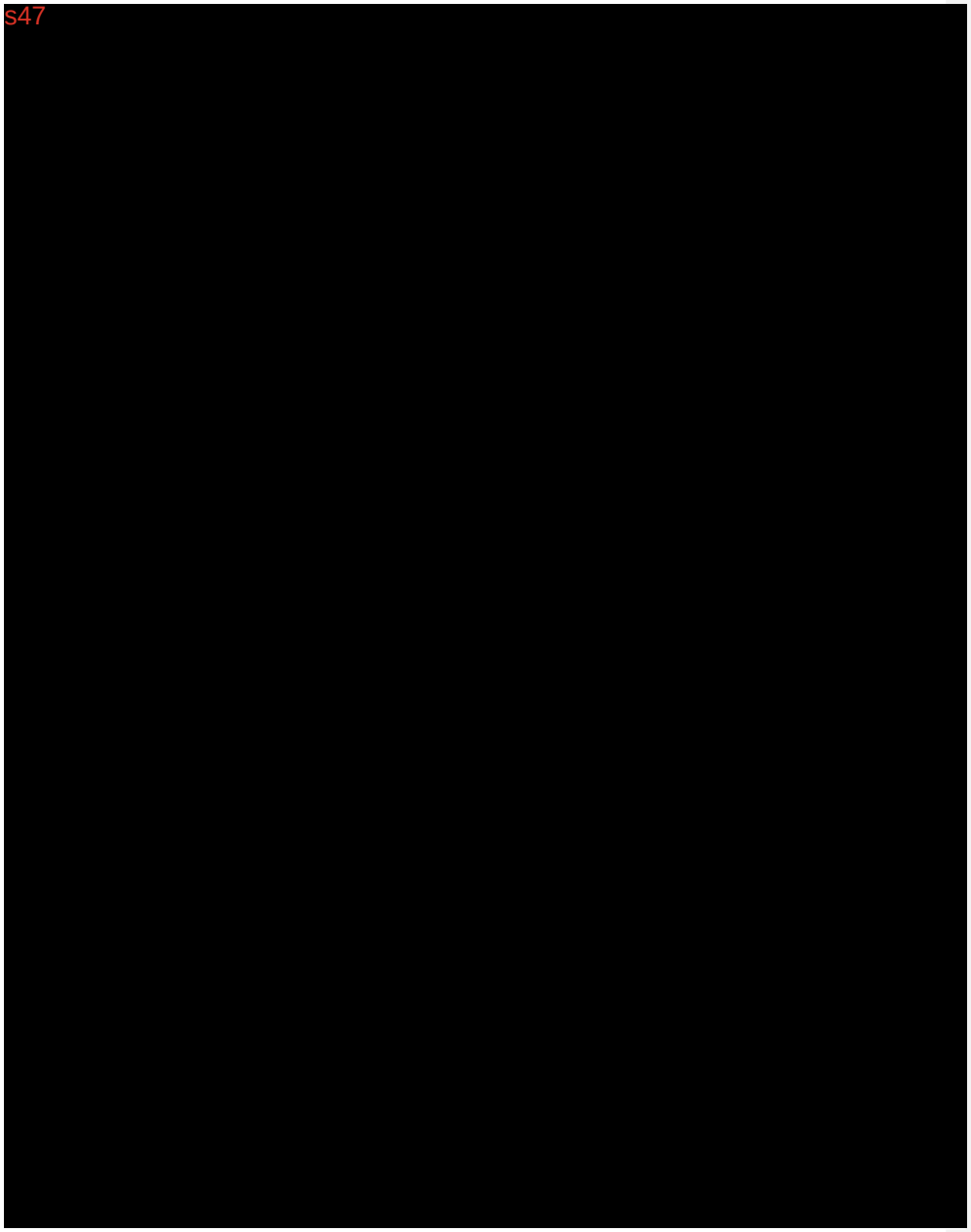

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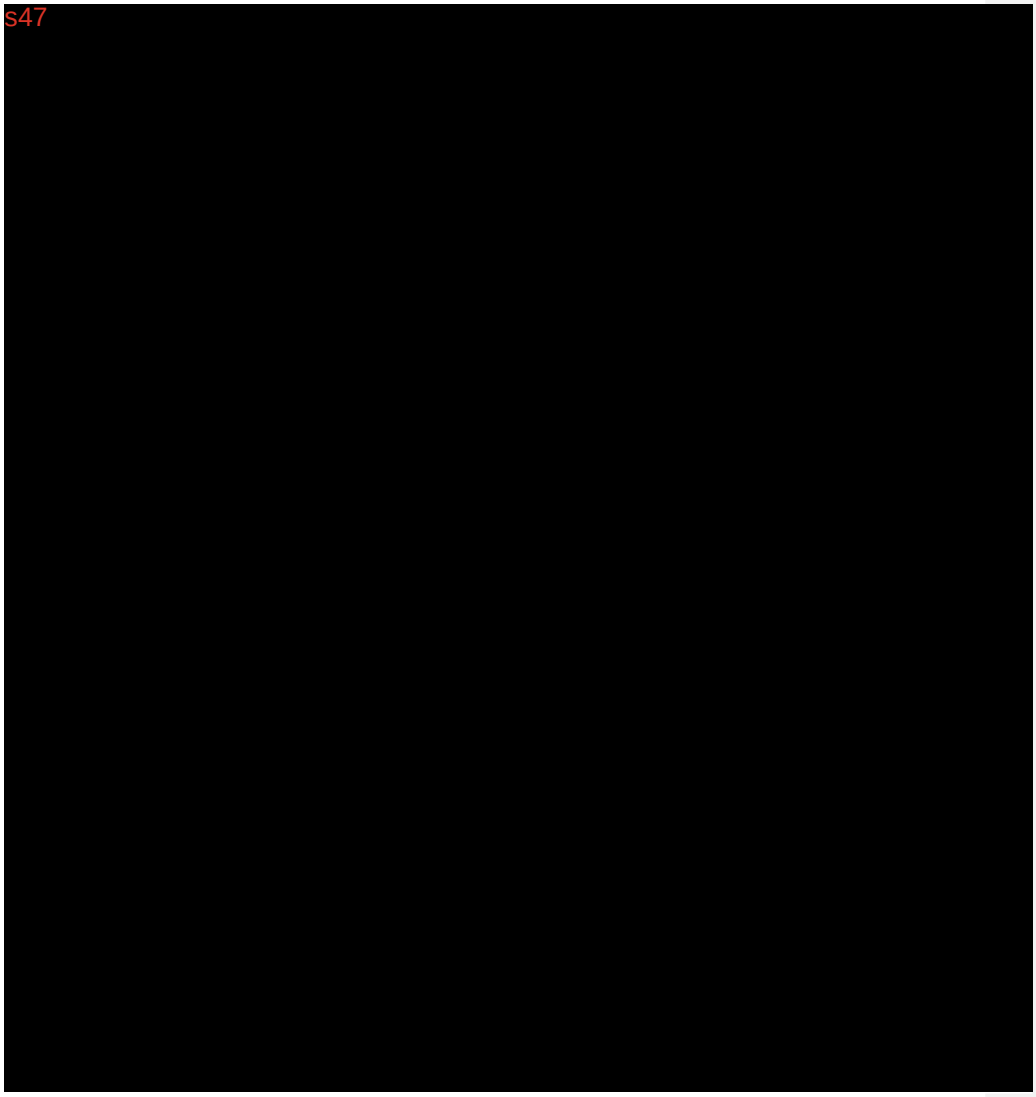

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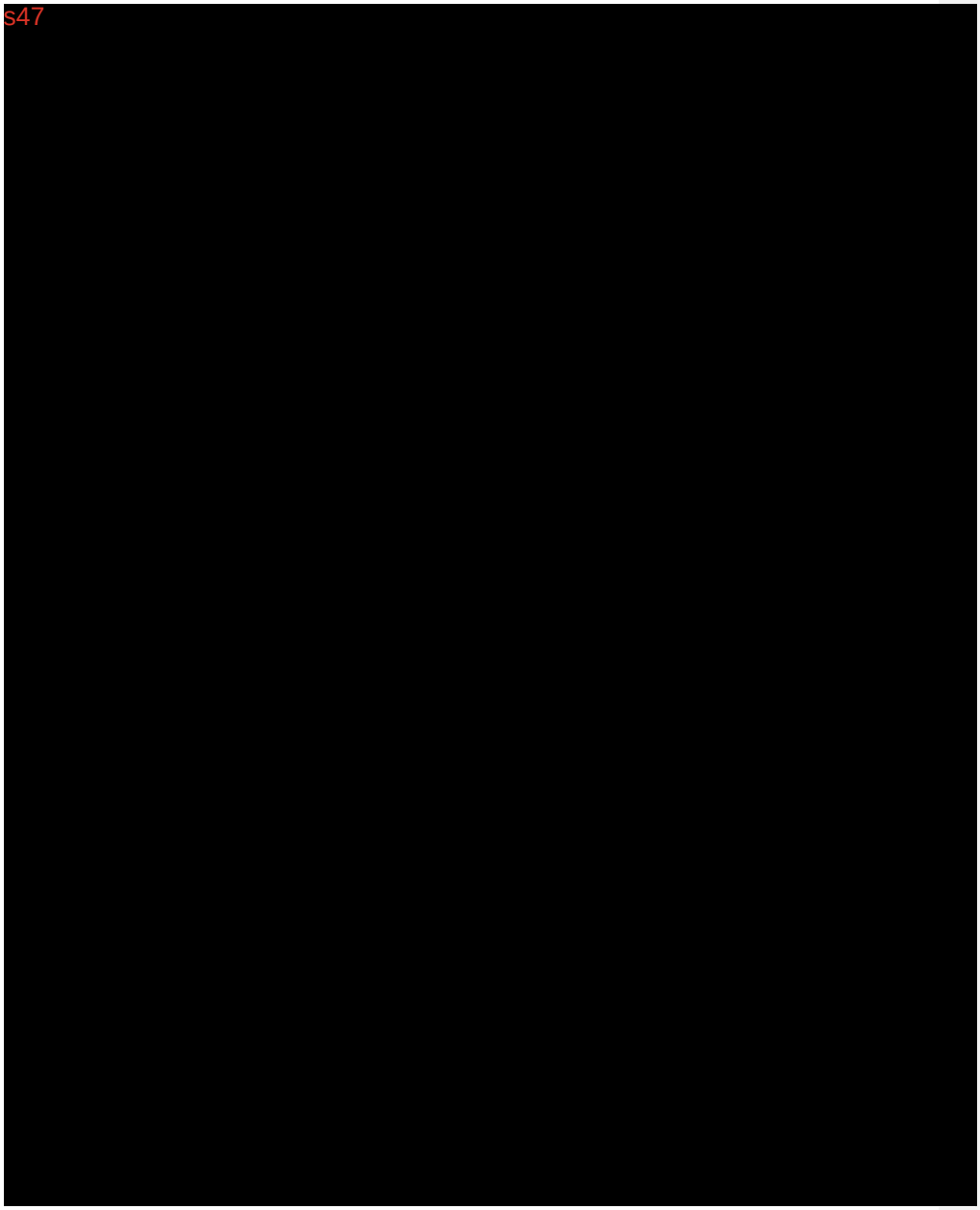

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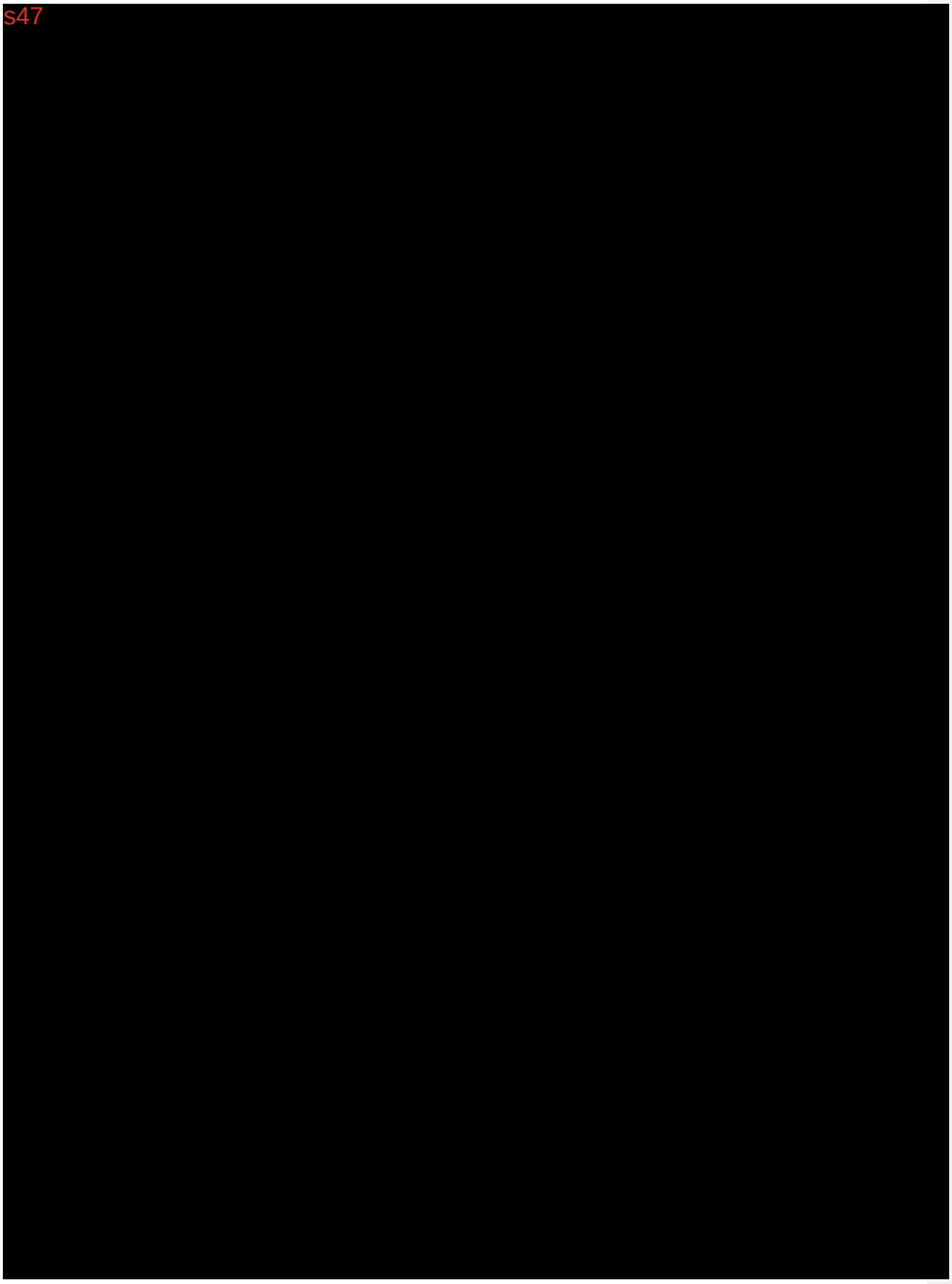

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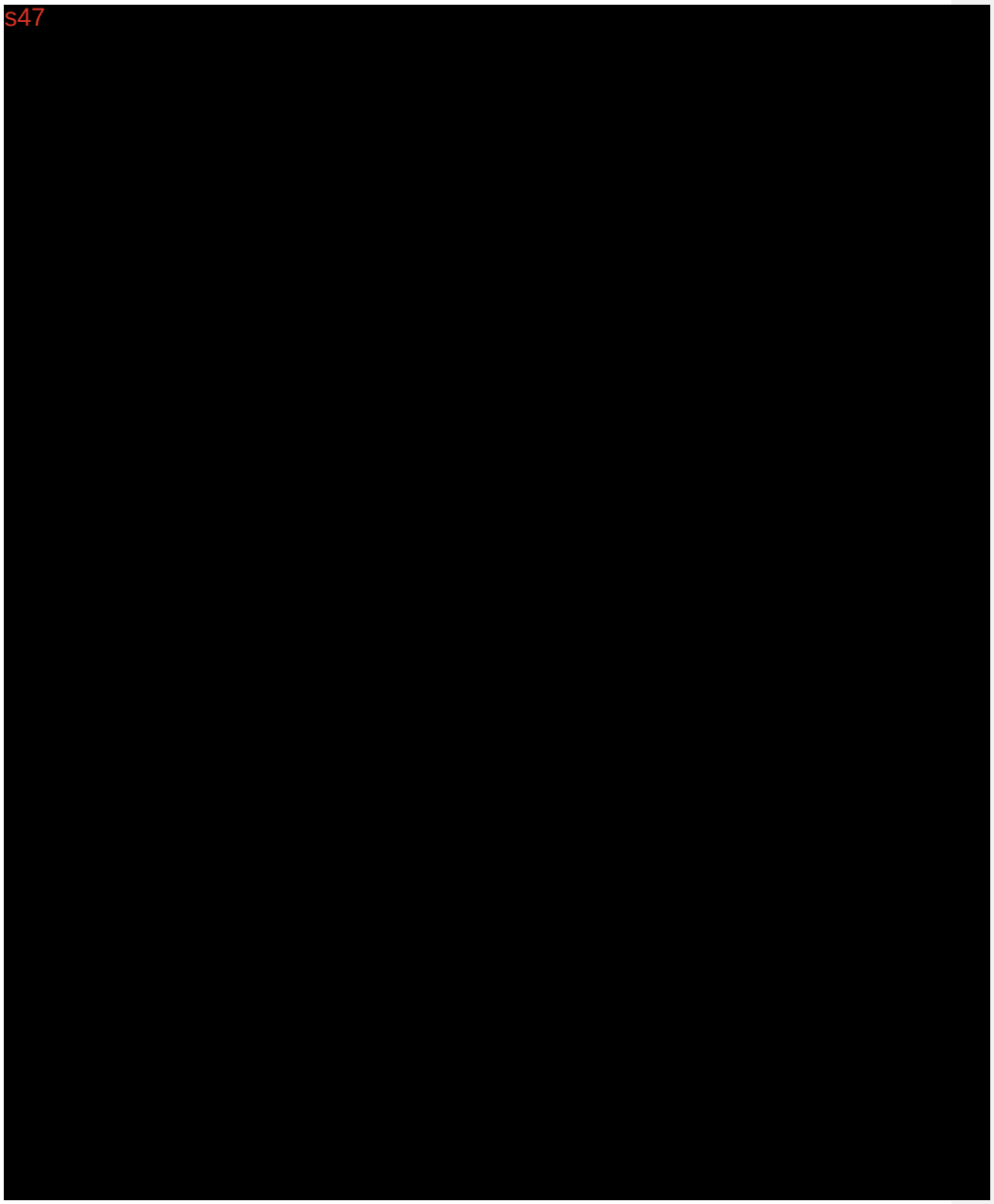

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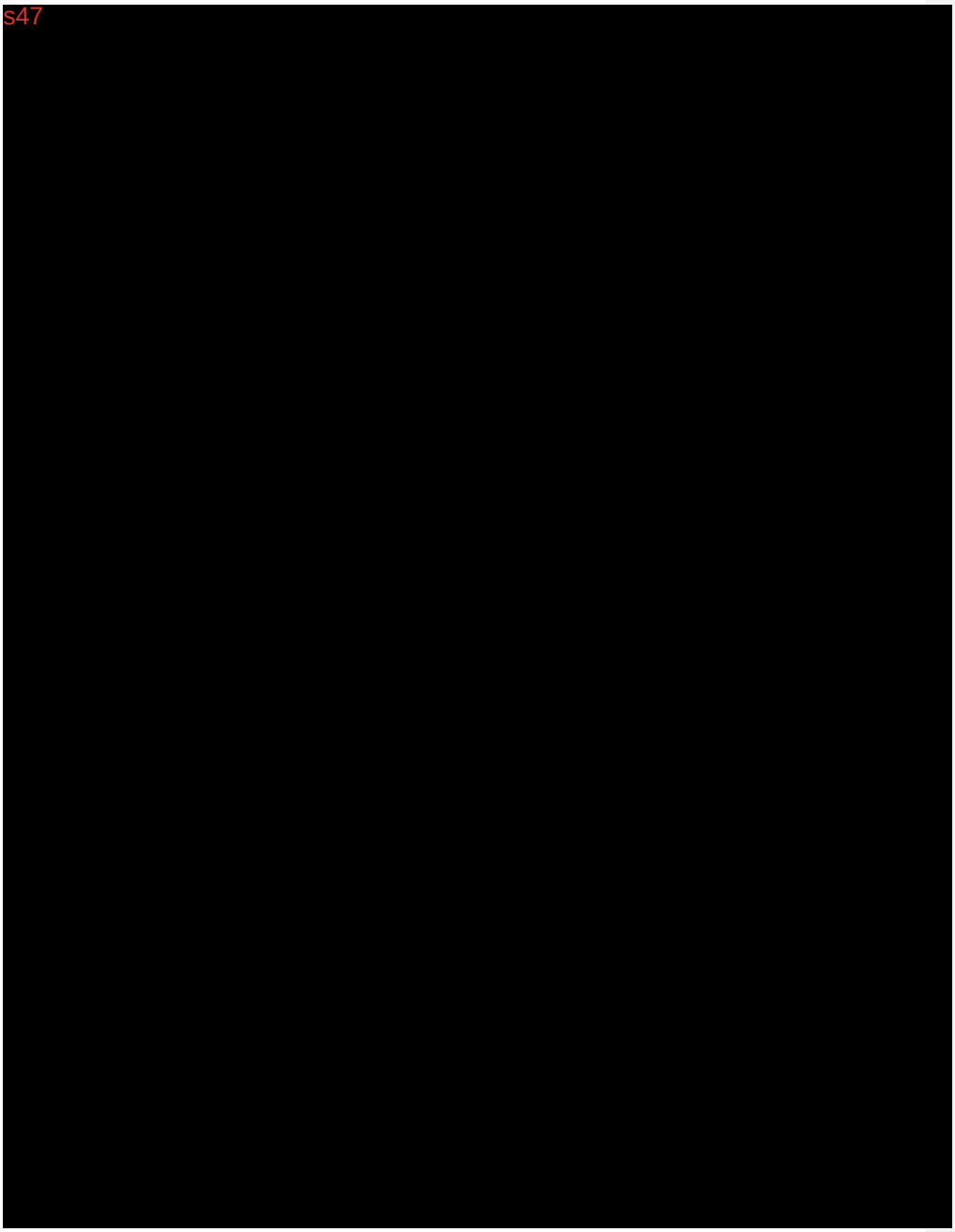

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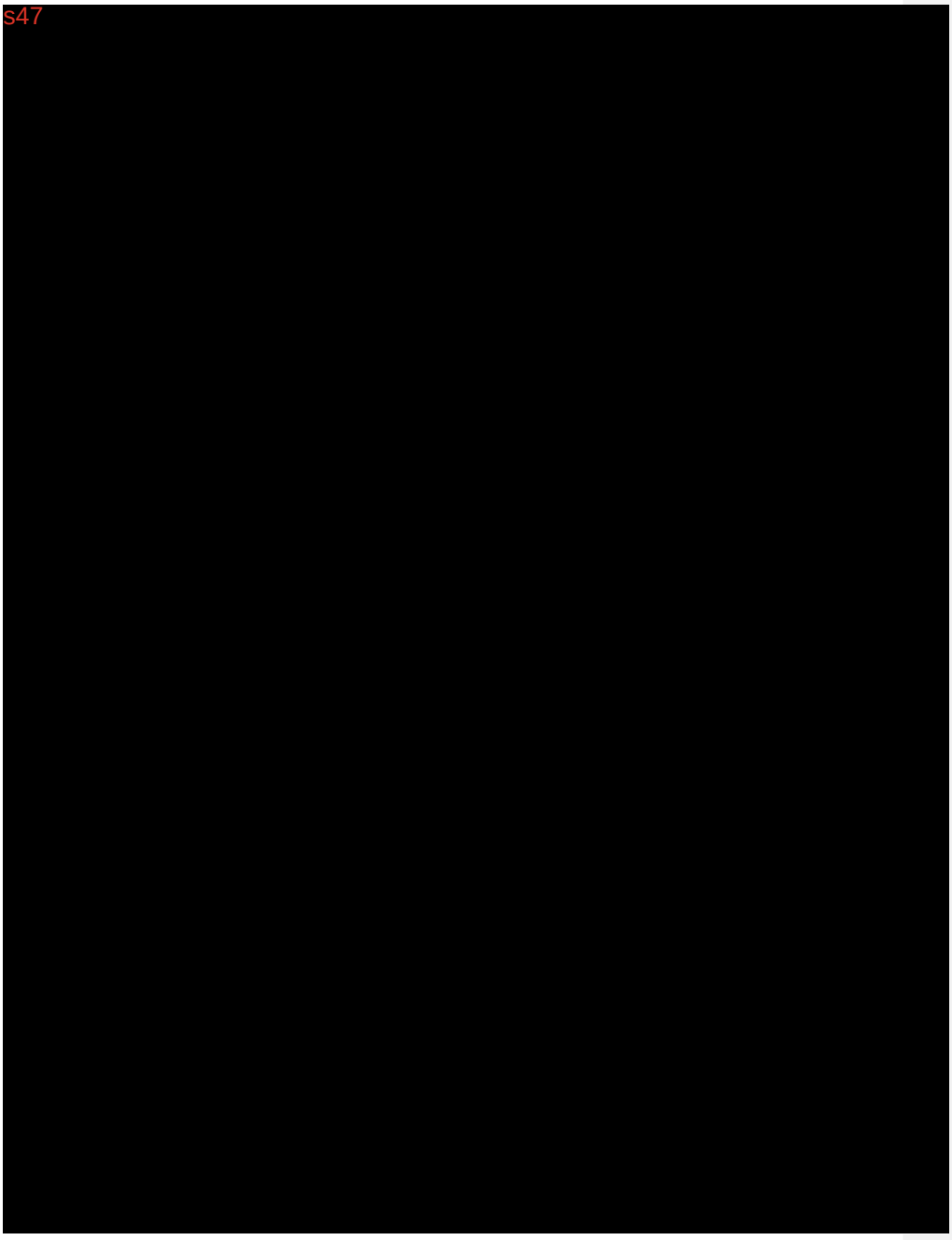

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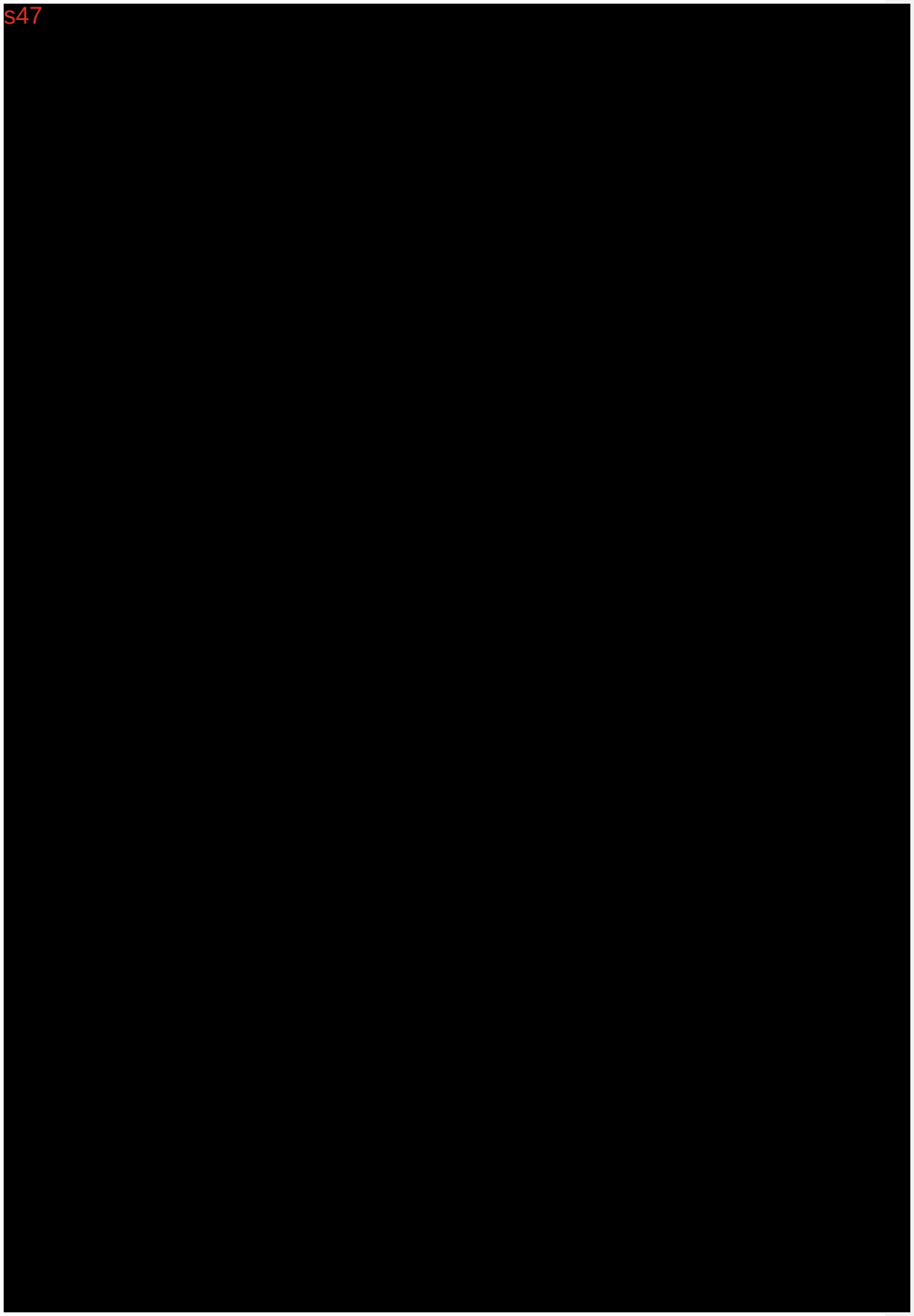

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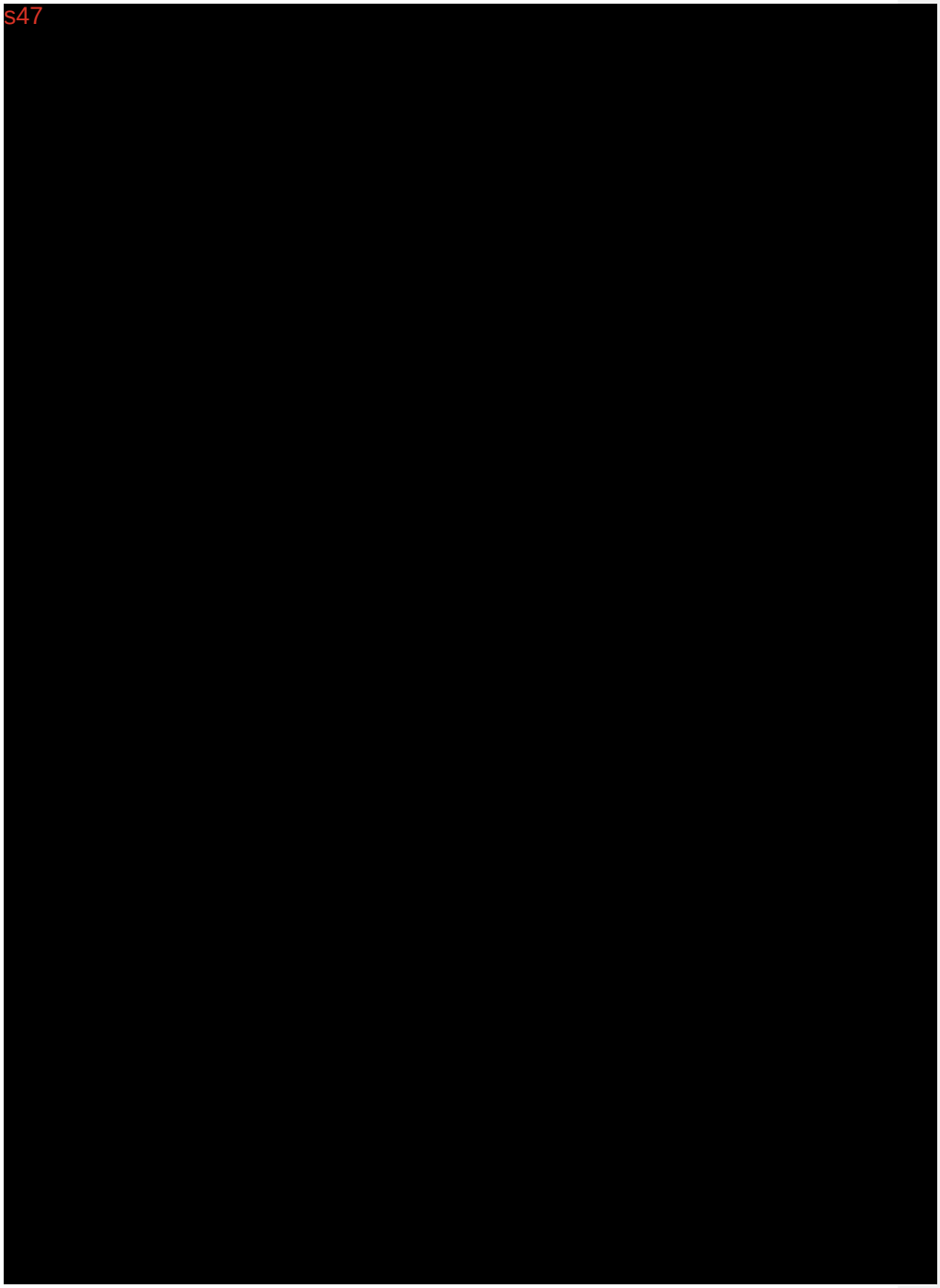

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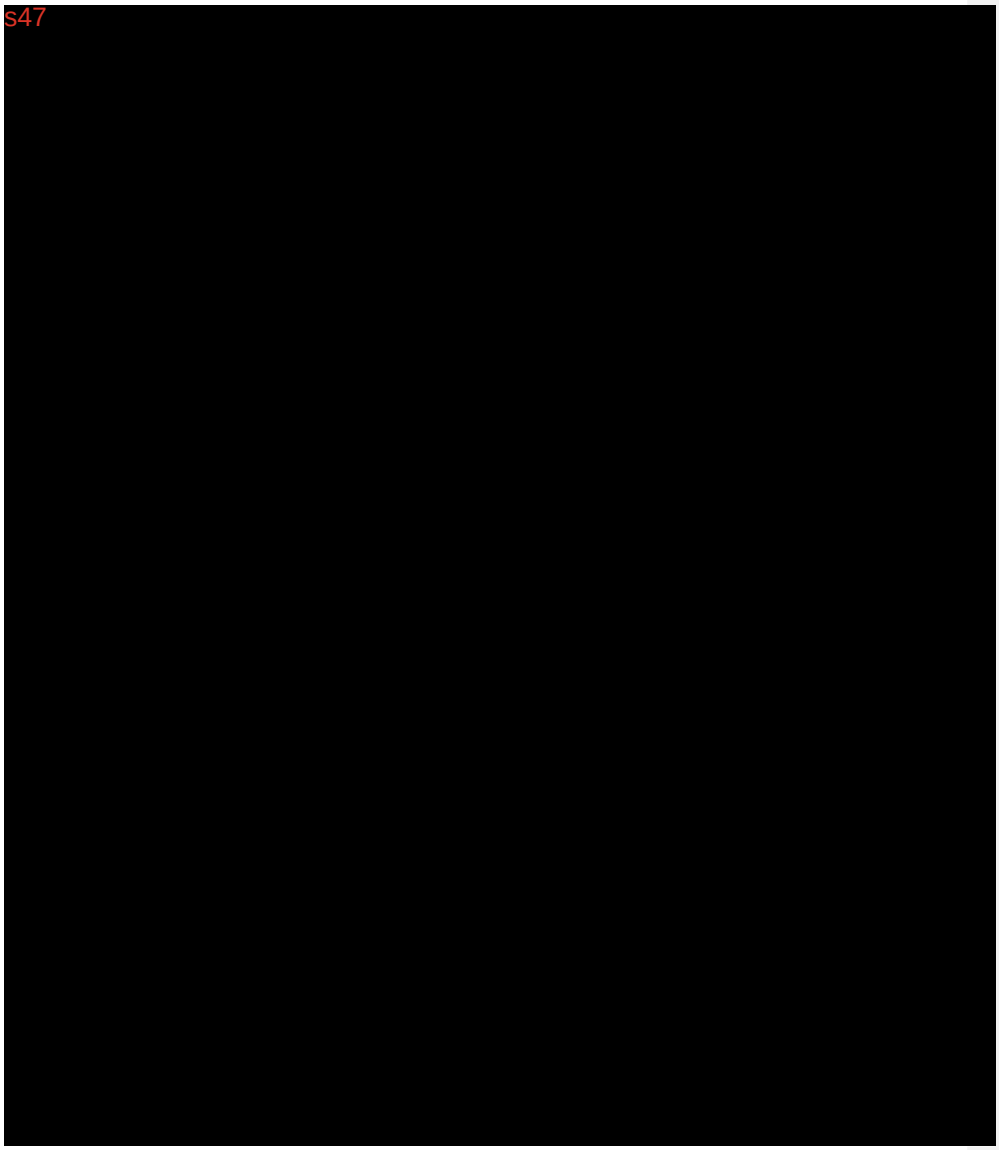

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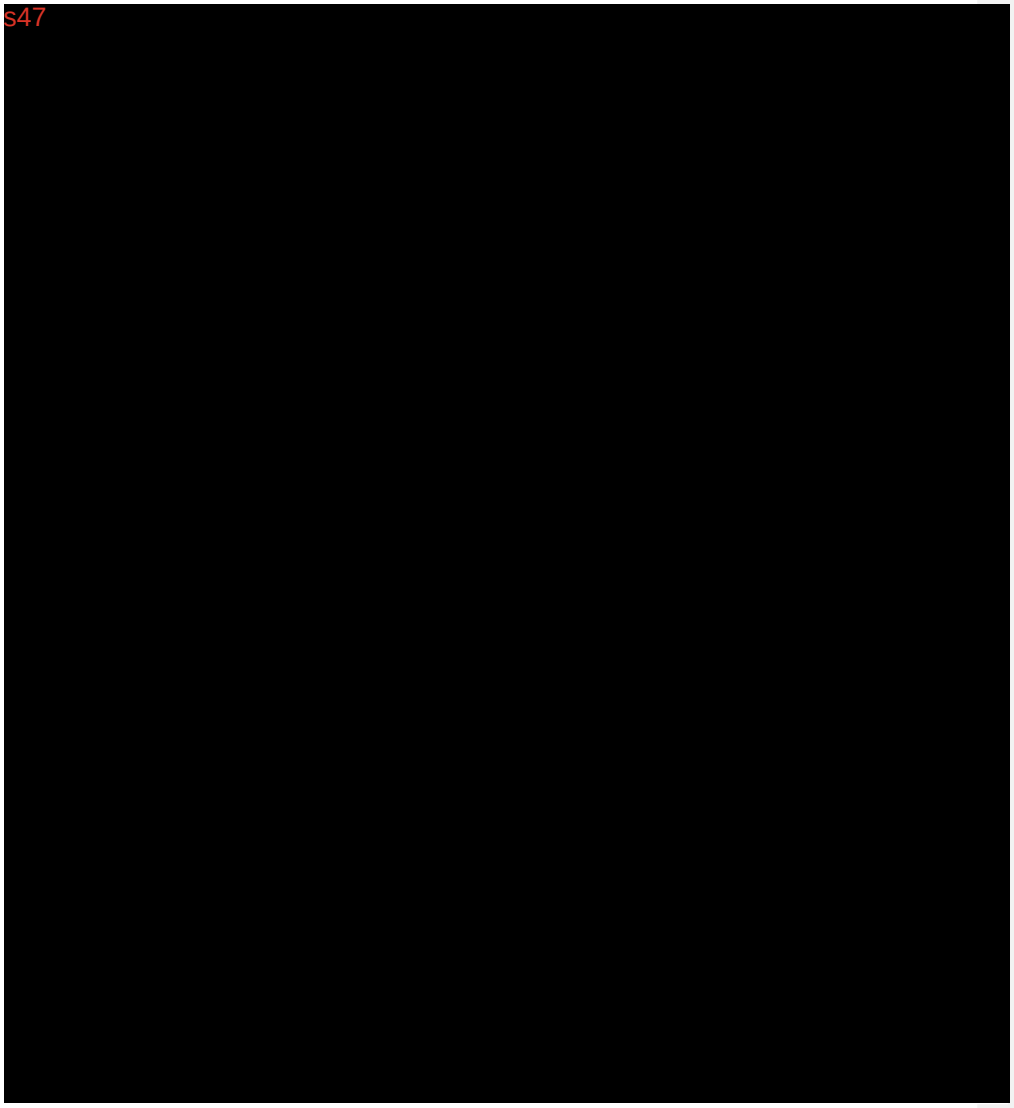

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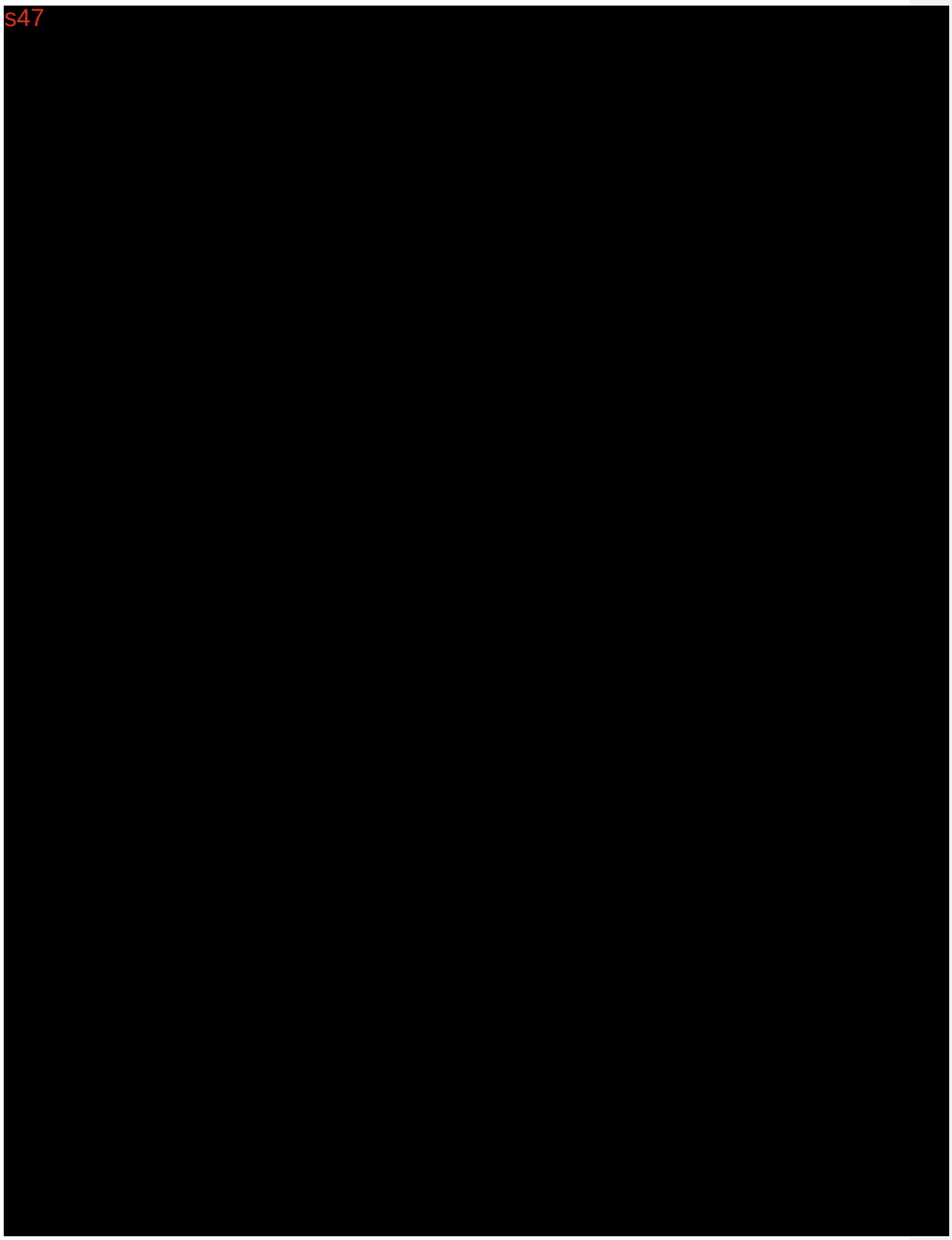

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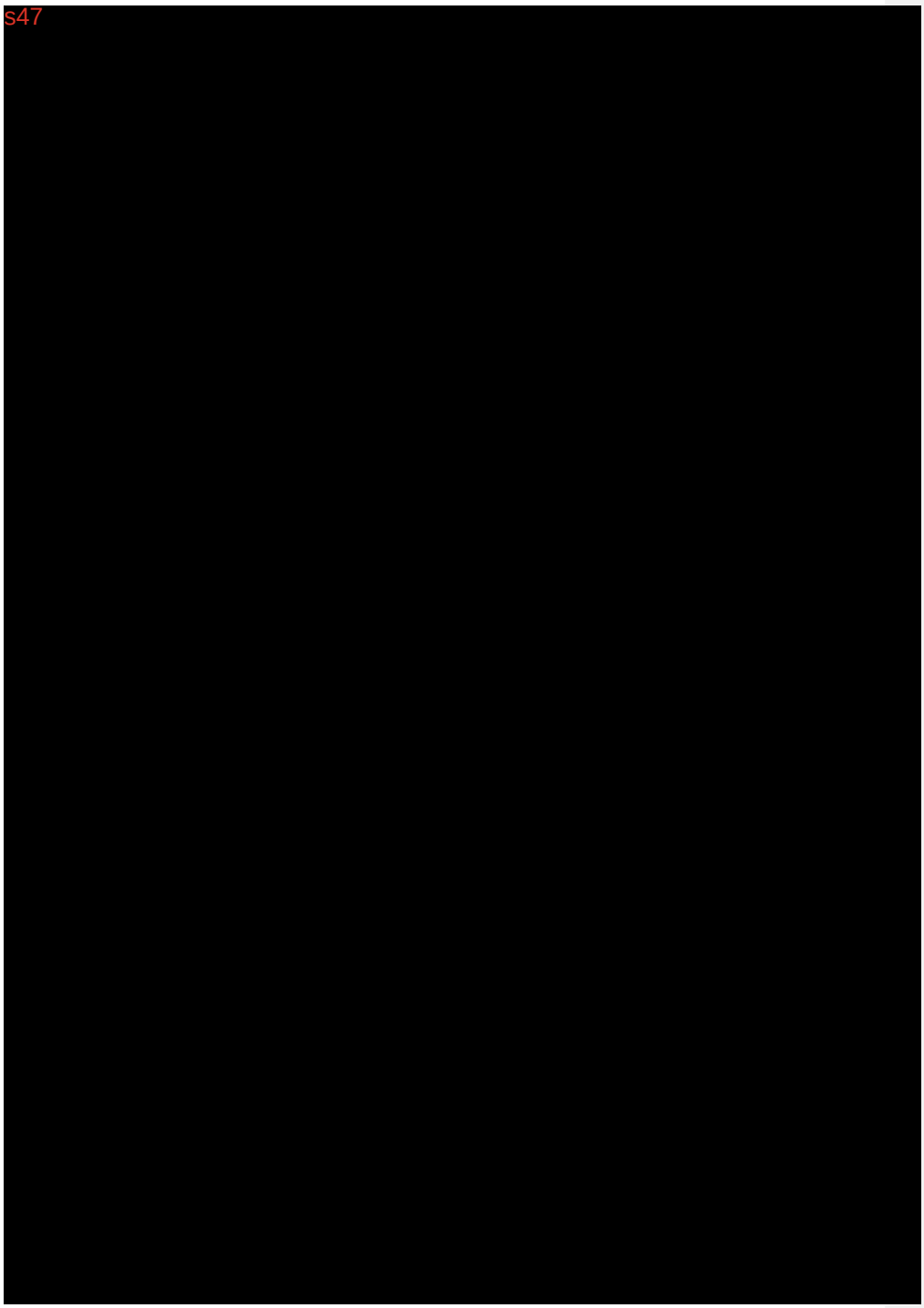

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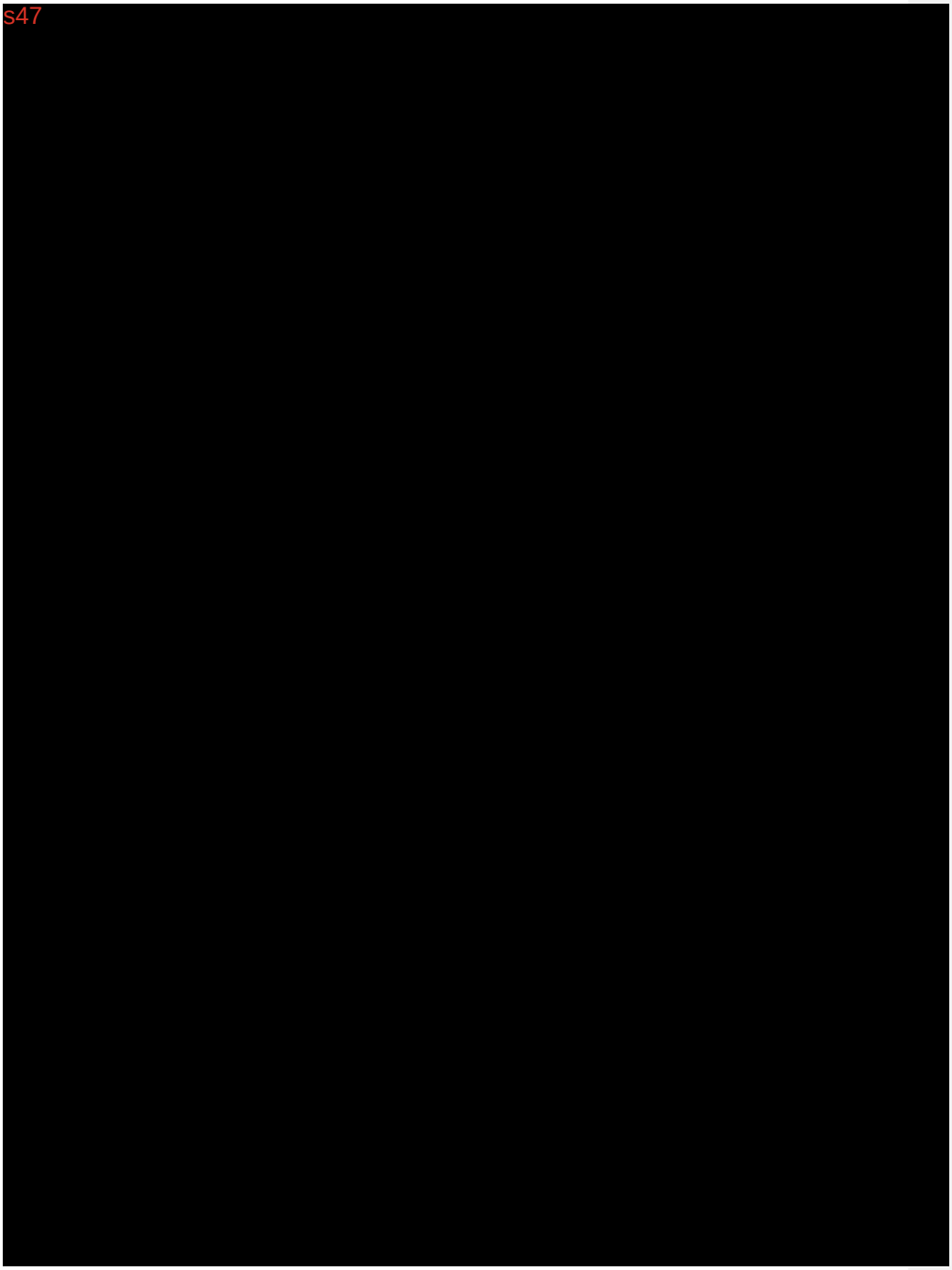

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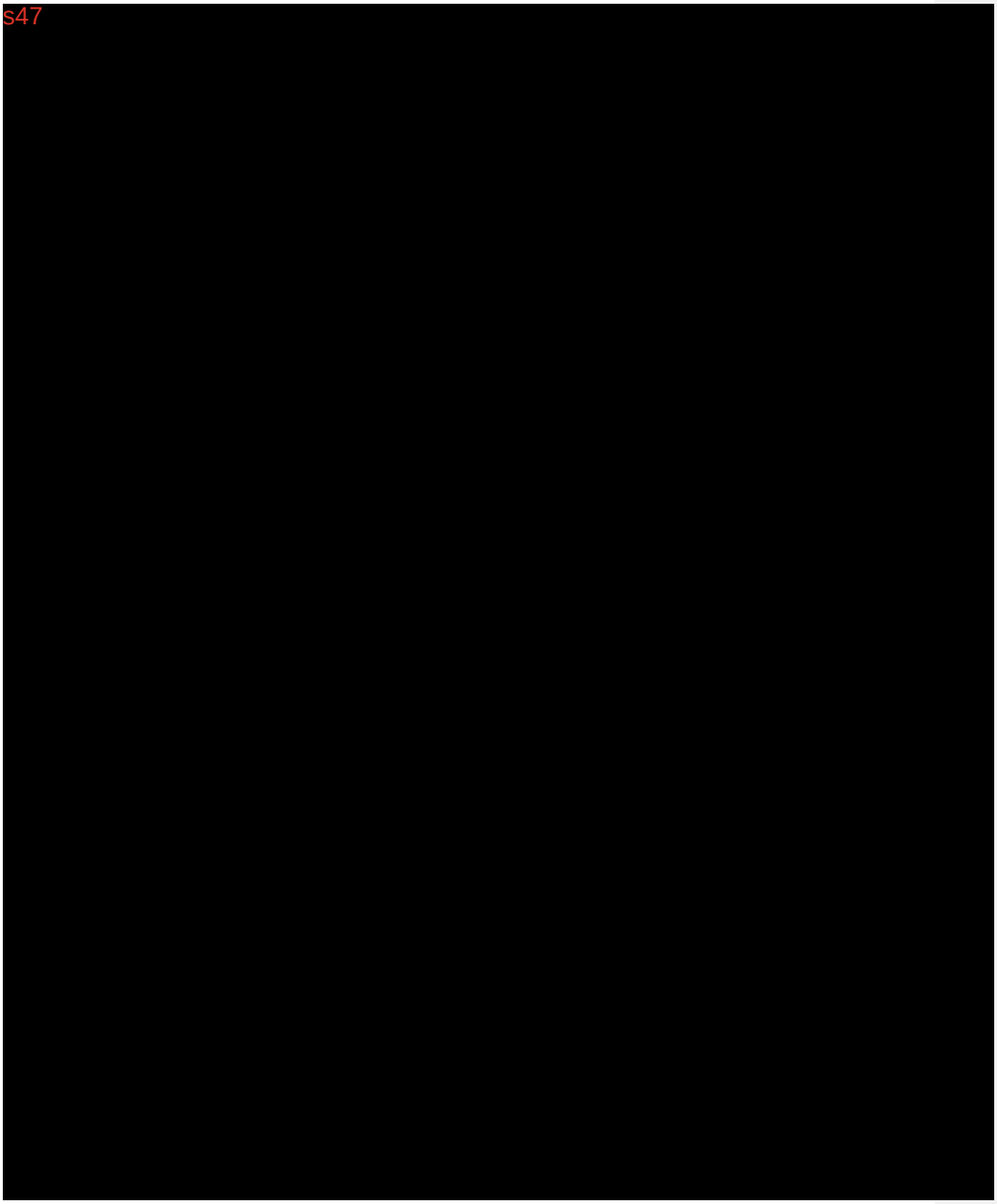

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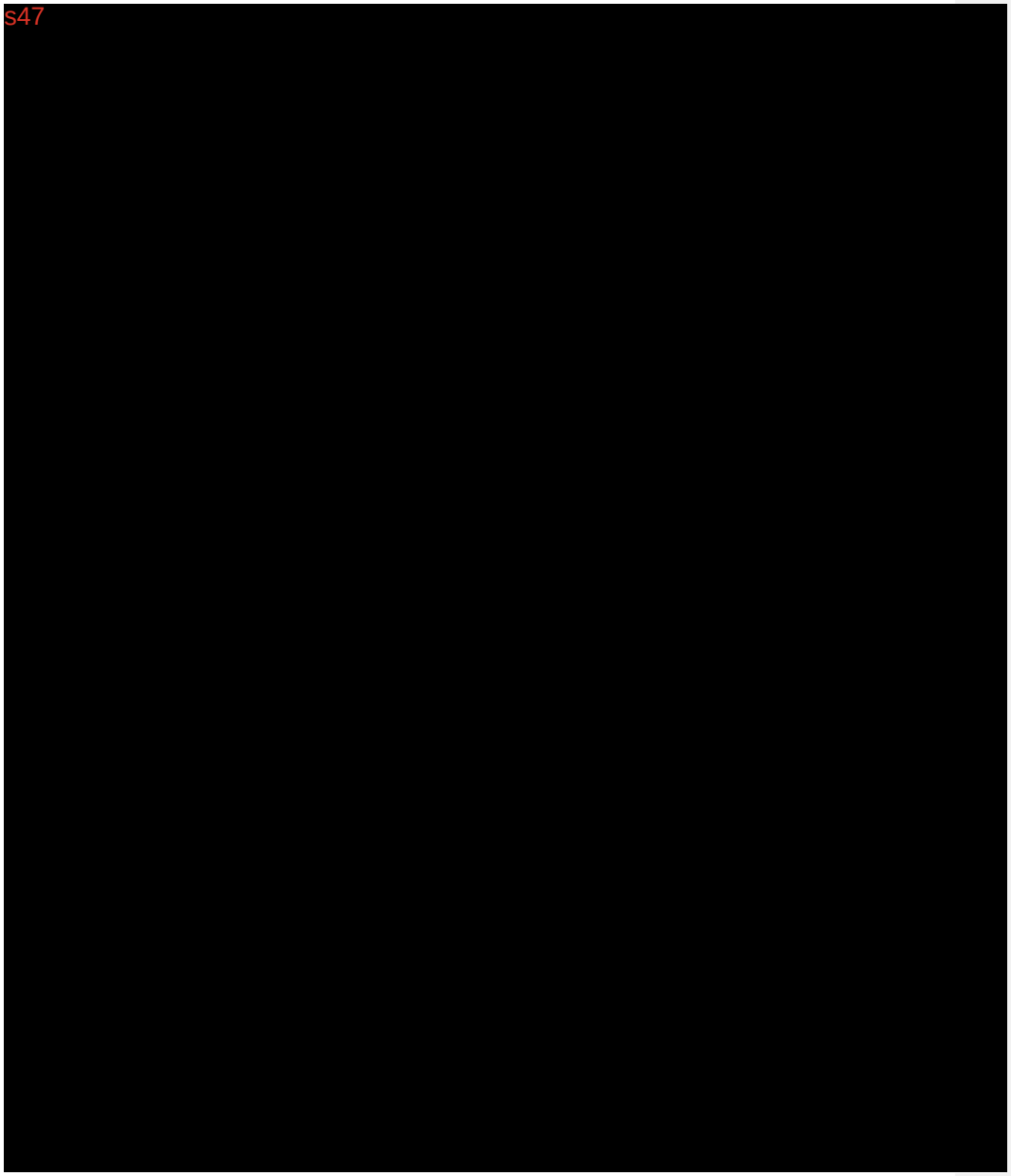

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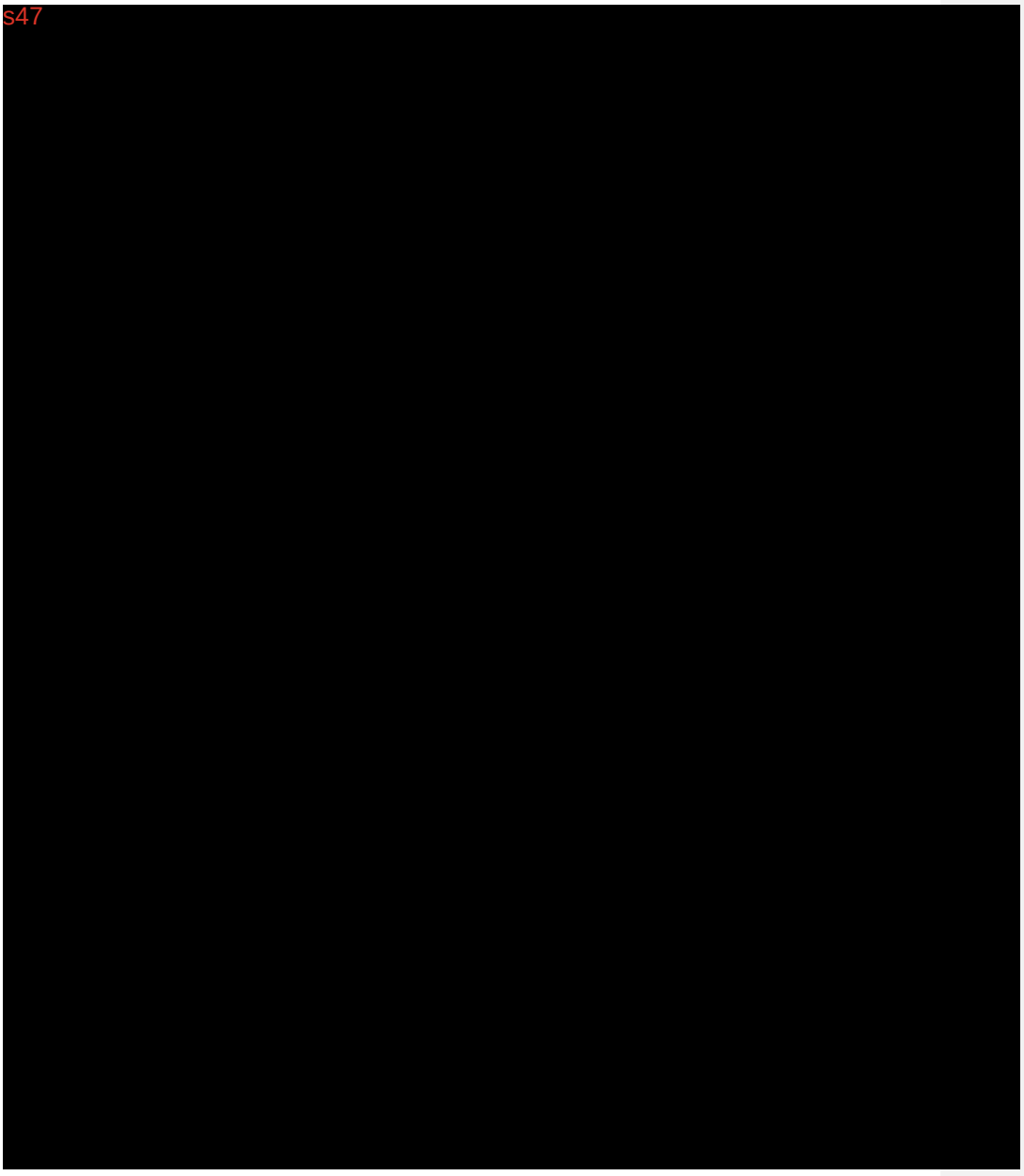

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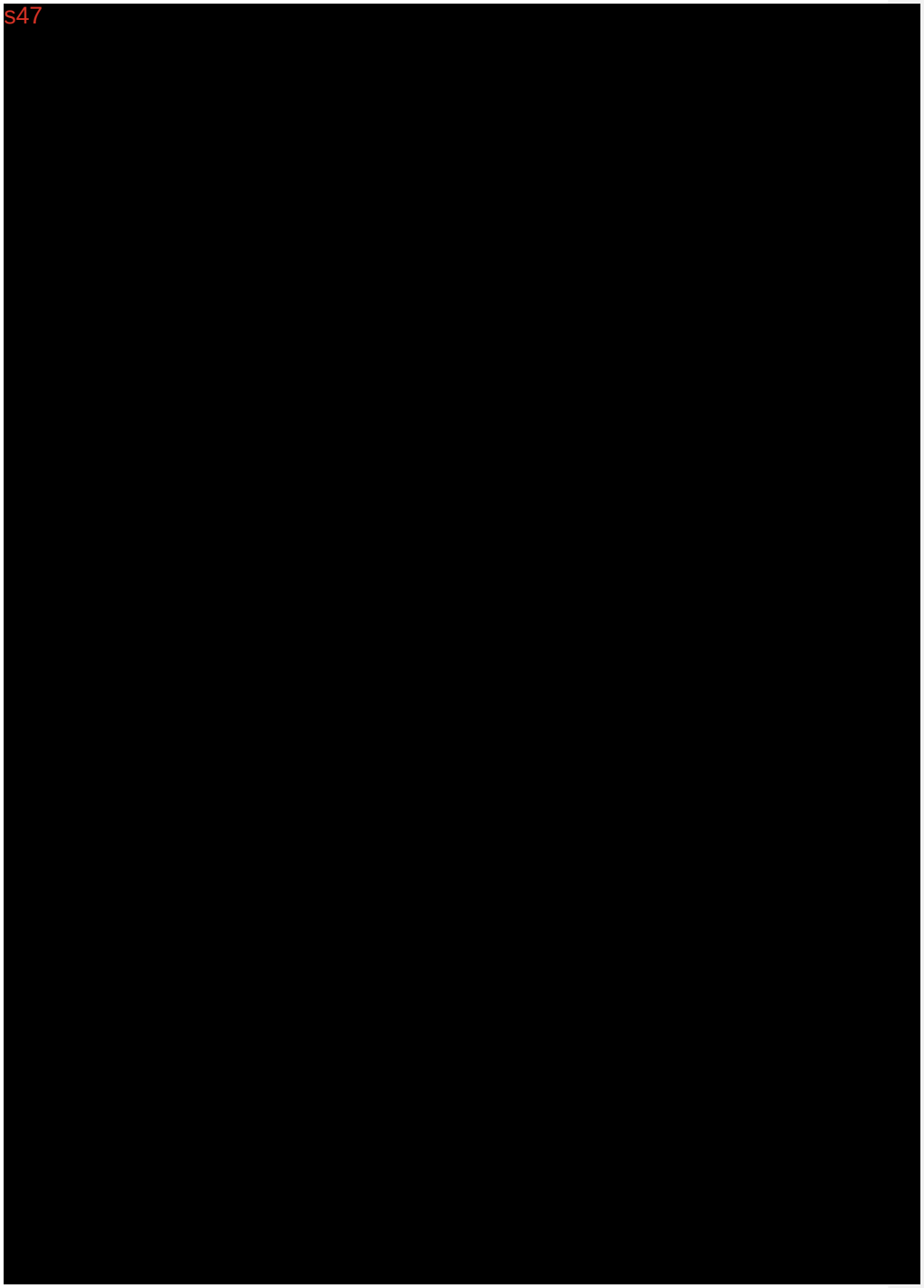

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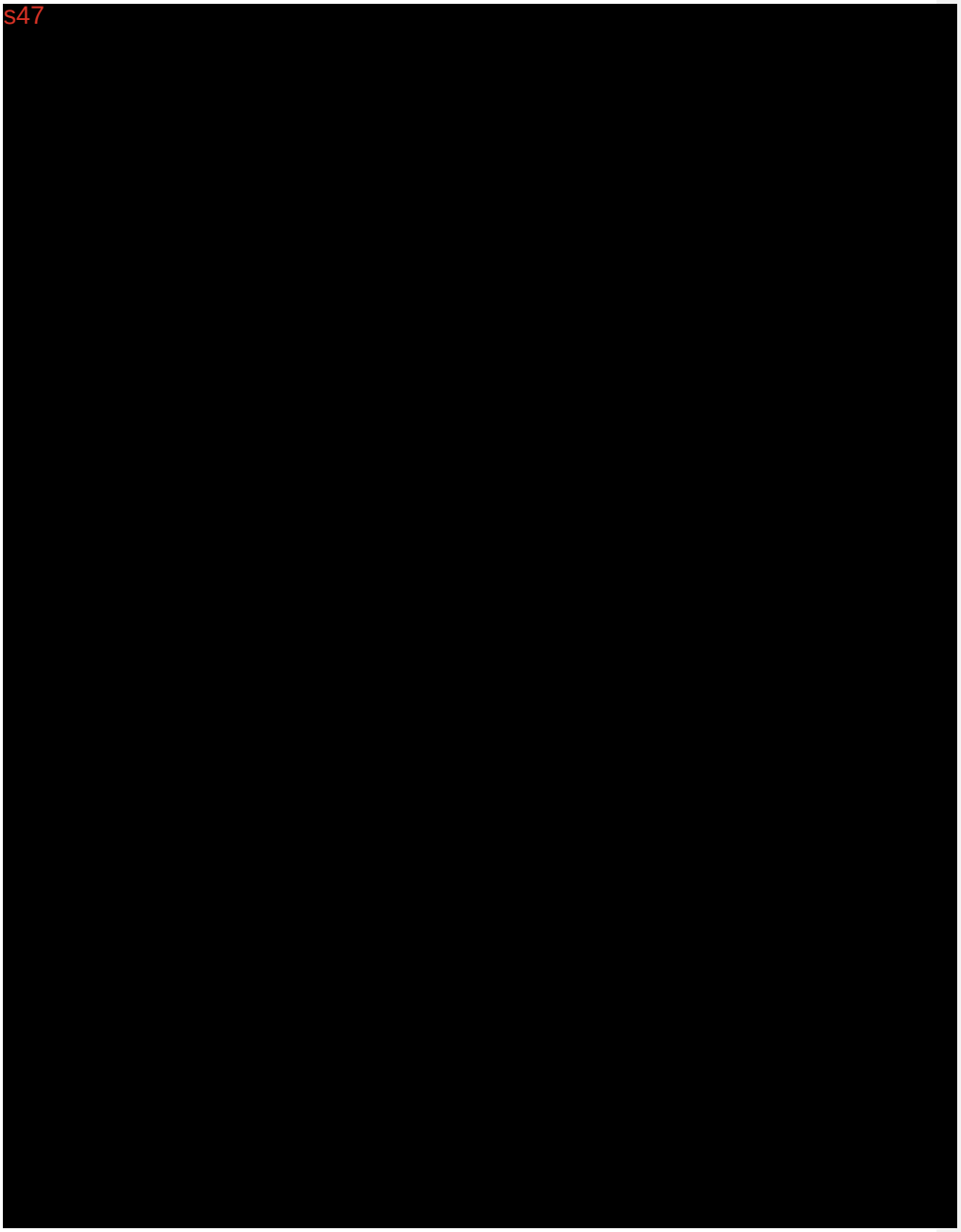

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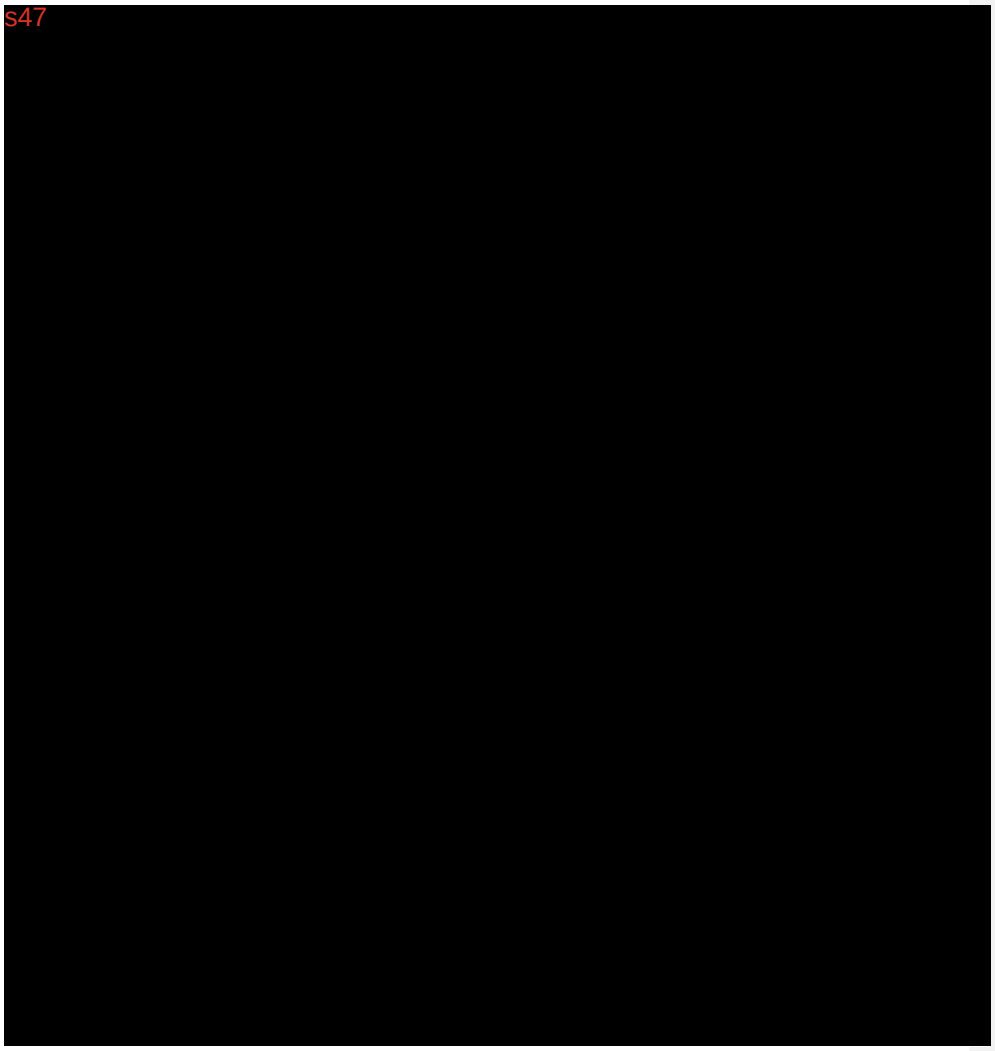

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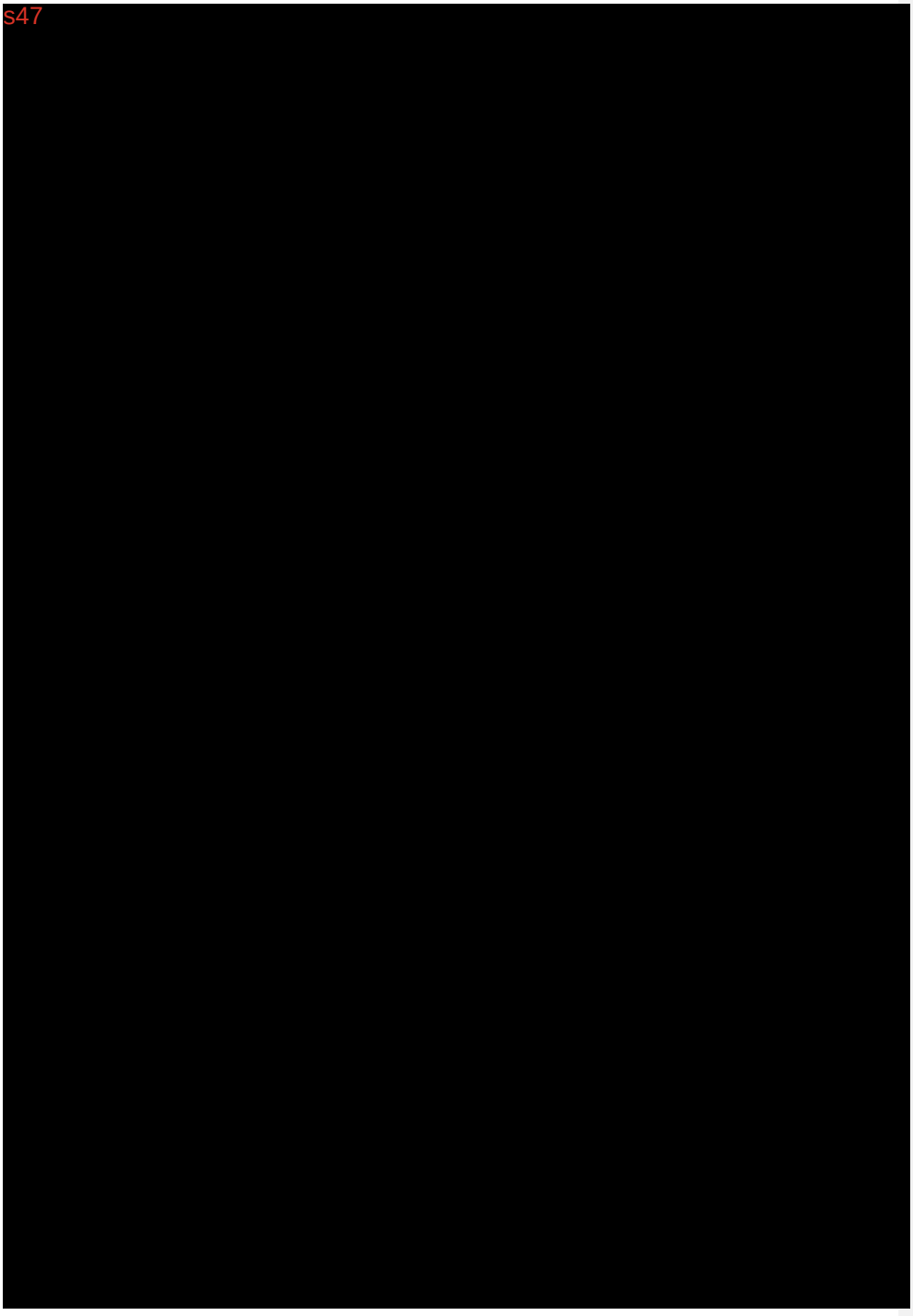

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Macaca fascicularis fact sheet

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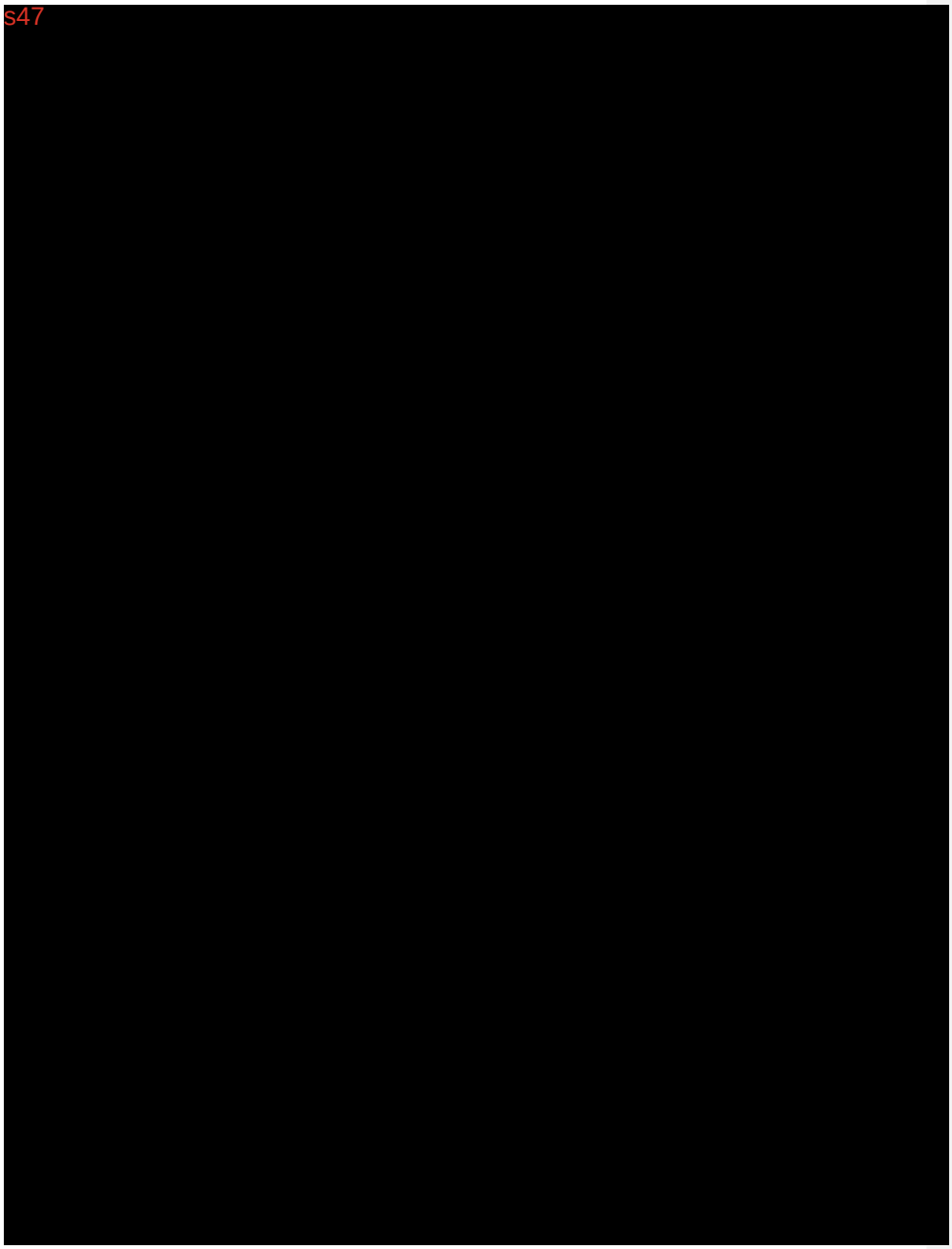

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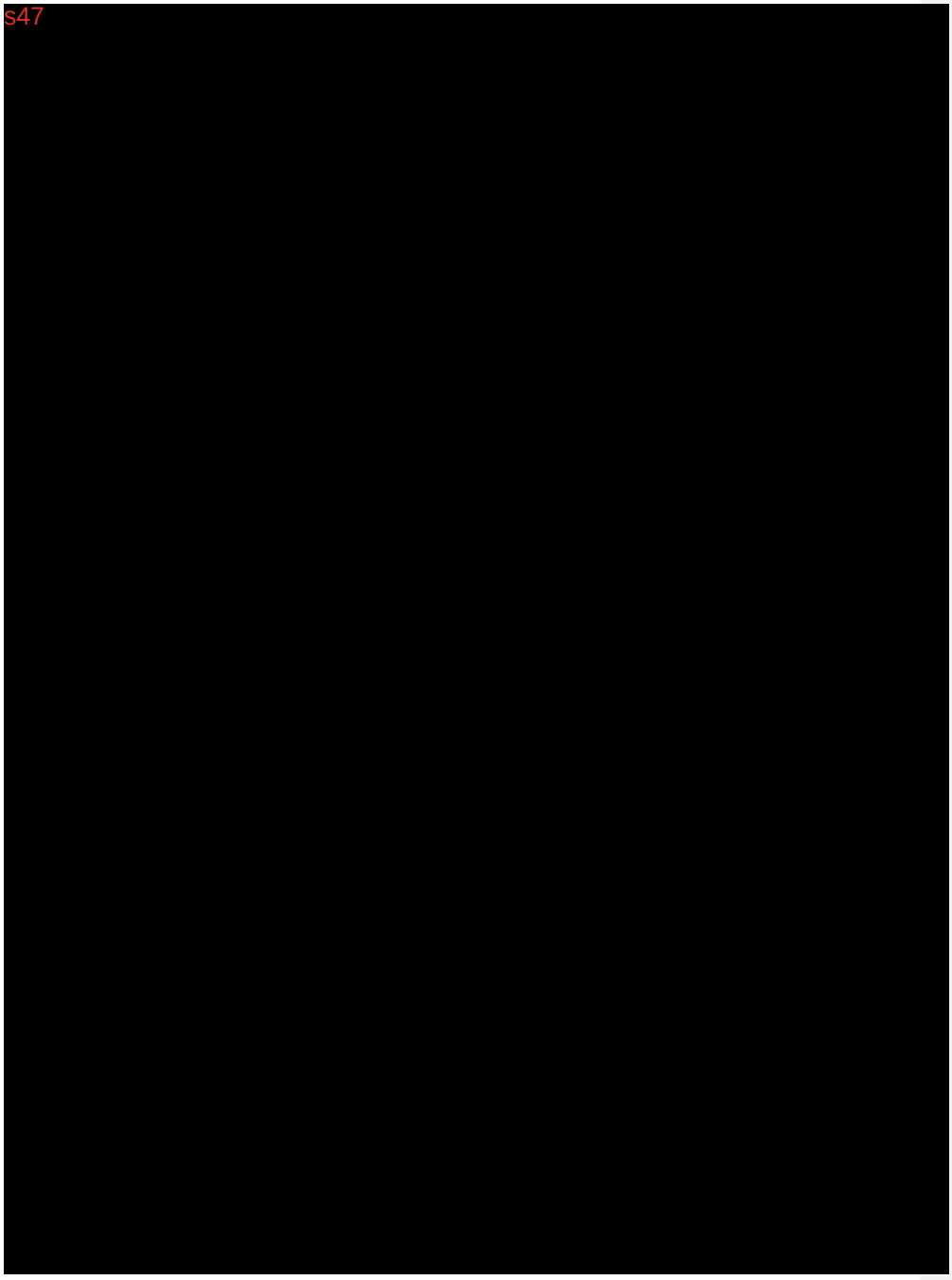

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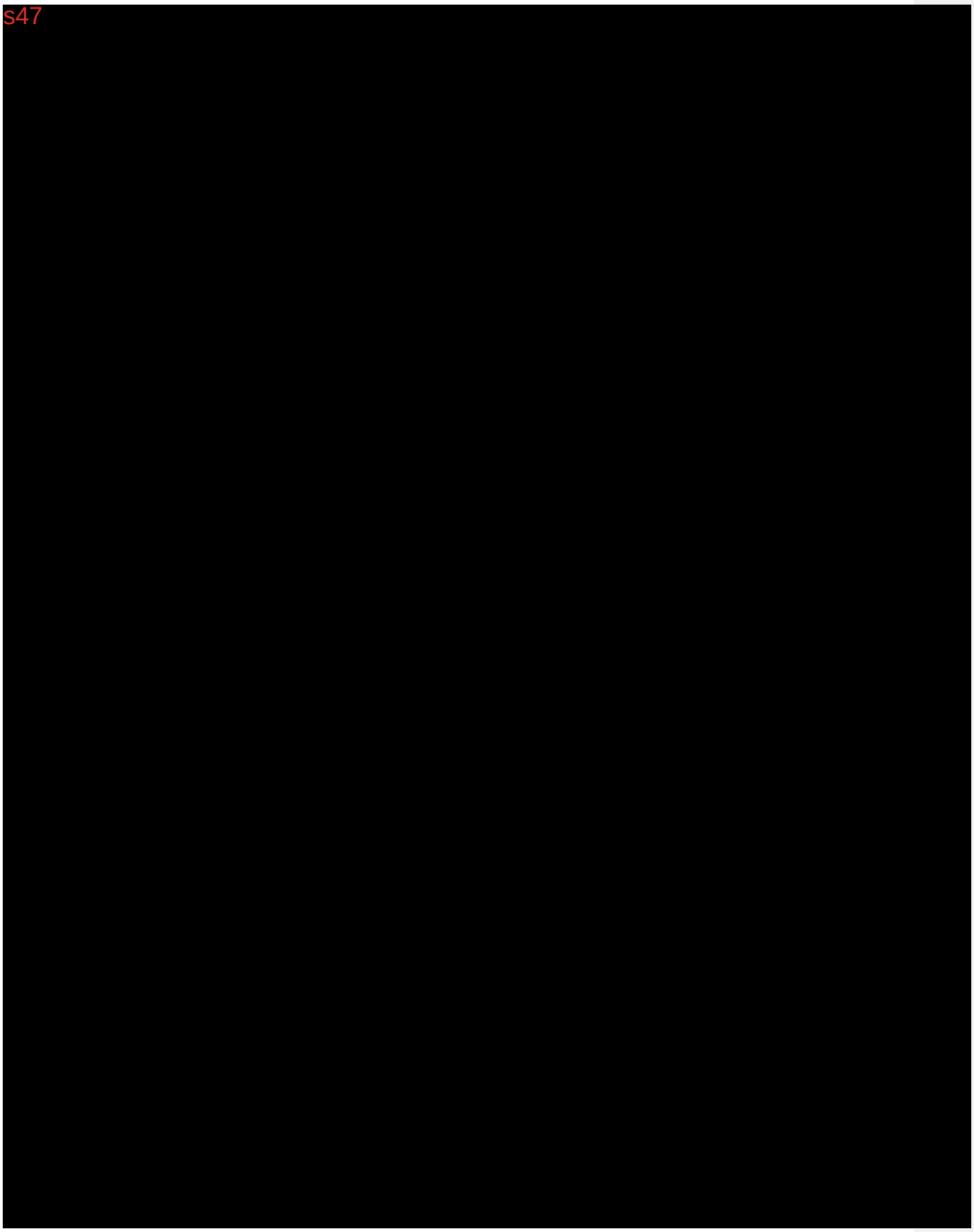

3. REPEAT-DOSE TOXICITY

A single study in NZW rabbit examining the toxicity of repeated doses of SARS-CoV-2 rS (NVX-CoV2373) with the adjuvant, Matrix-M1 was submitted (Table 3.1~~Table 3.1~~). Since this submitted study did not include an adjuvant only test group, additional supporting studies (in SD rats and NZW rabbits) non-SARS-CoV-2 antigens and Matrix M1 were provided for evaluation of the toxicity for the adjuvant, Matrix-M1. All the studies were GLP–compliant. Studies 37348 TSR, 161014 and 2088-13549 are not evaluated due to the absence of test item concentrations details or the lack of adjuvant only test groups.

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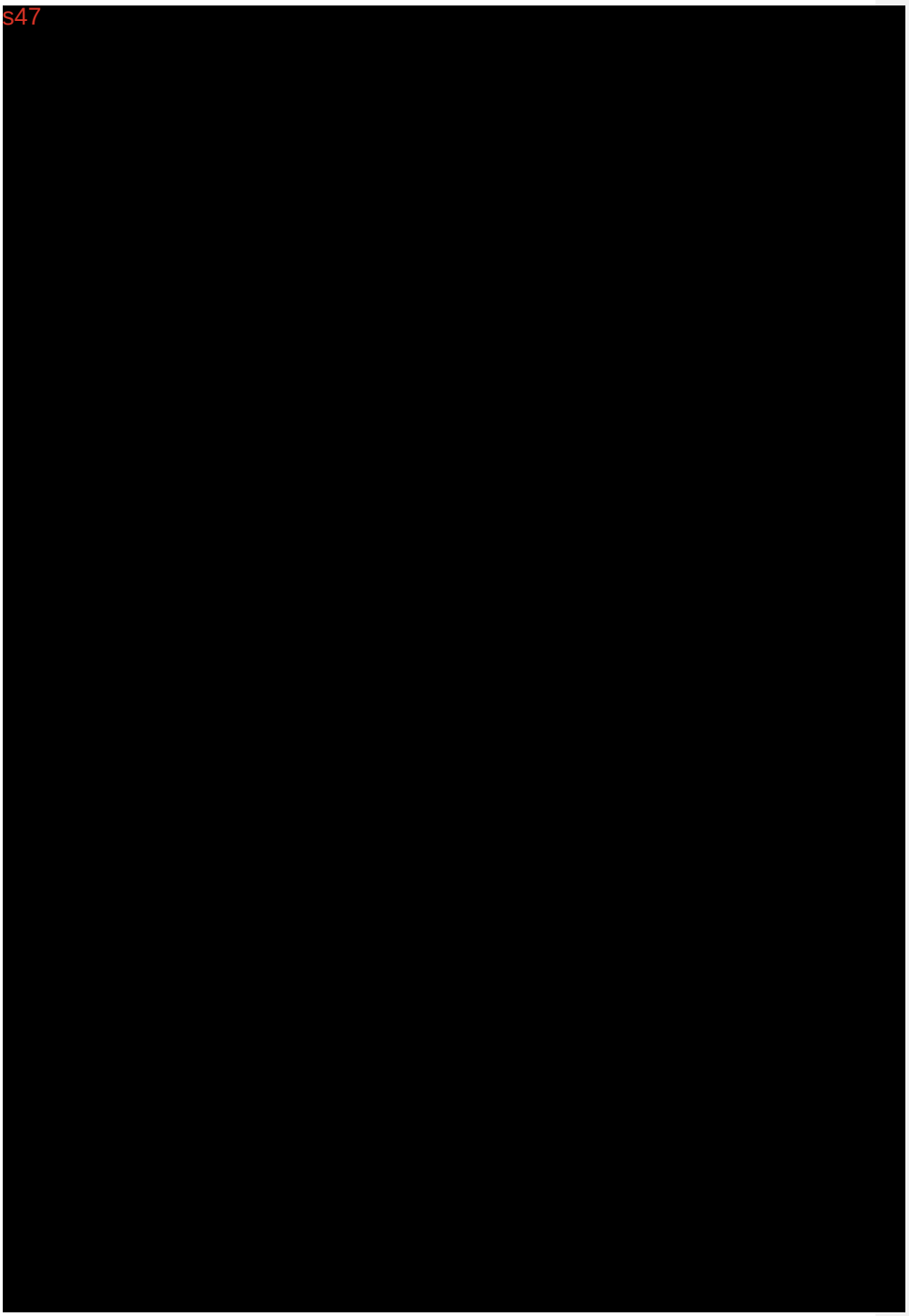

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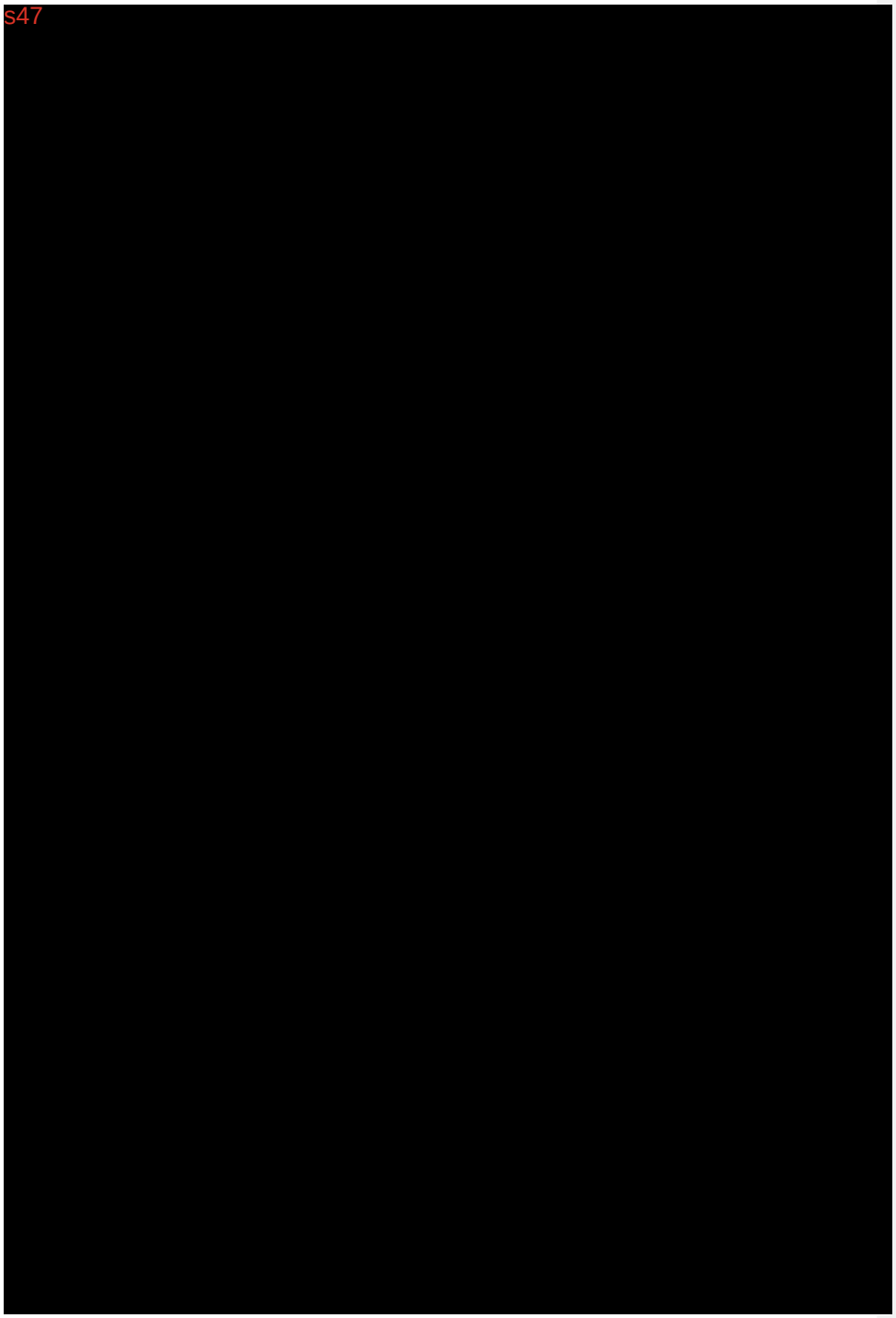

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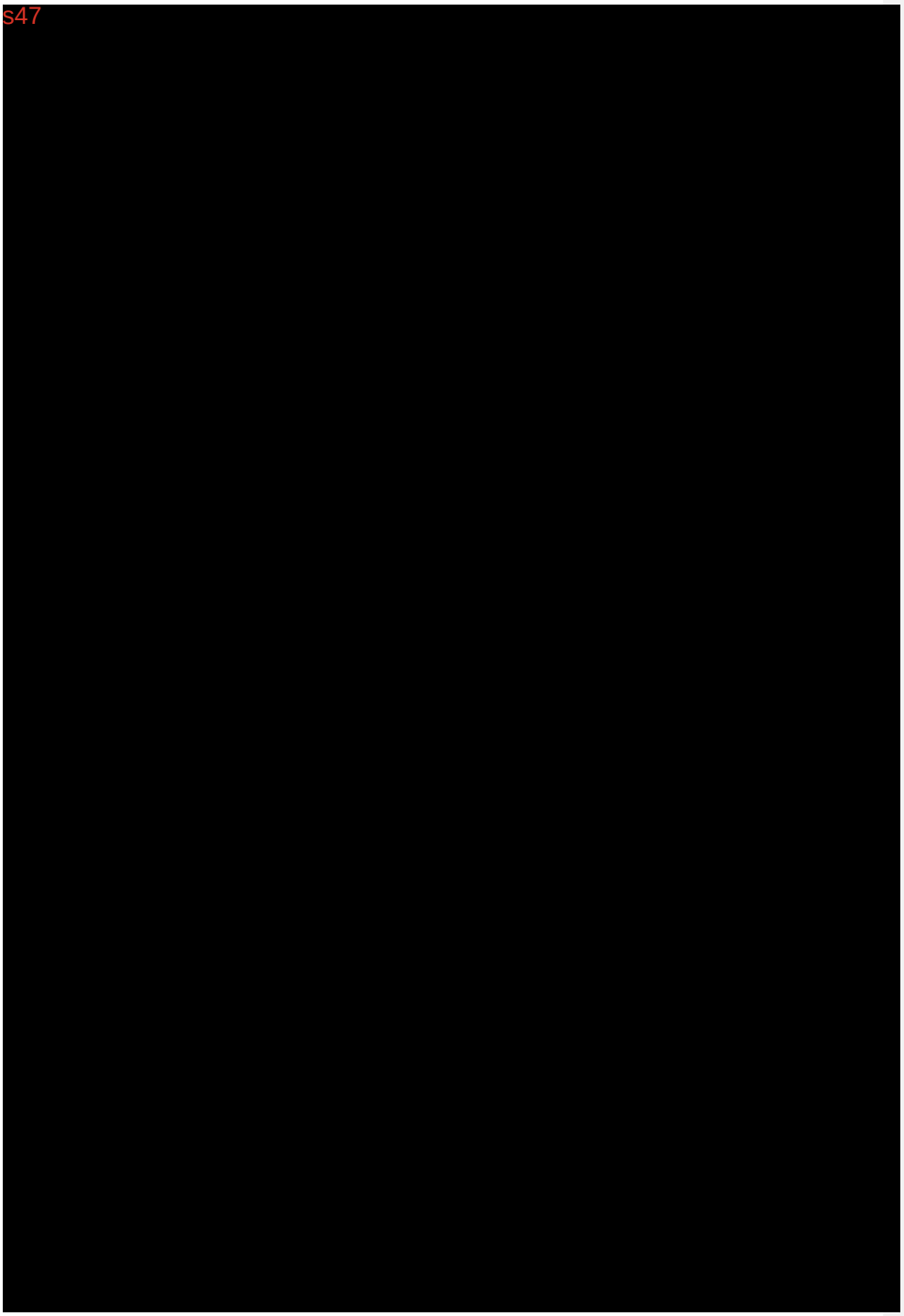

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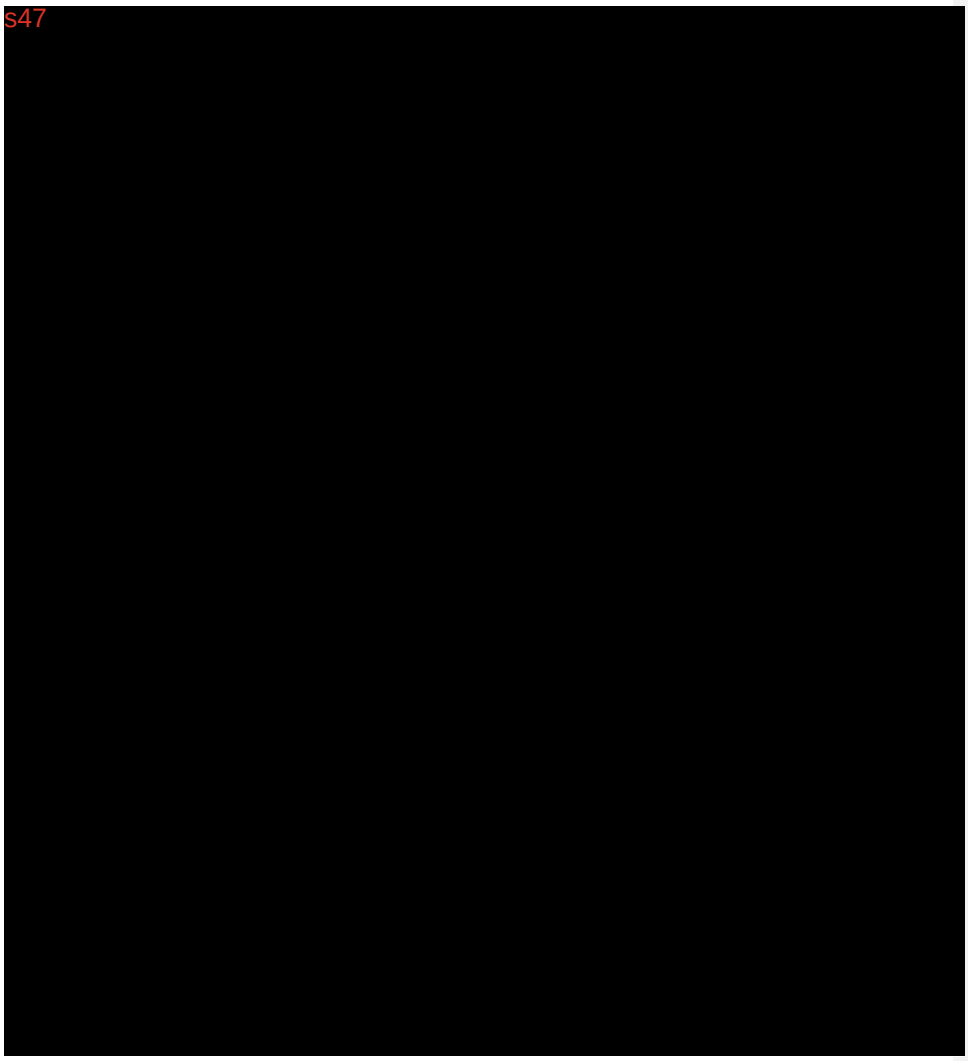

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4. GENOTOXICITY

The submitted genotoxicity studies on Matrix-M1 included two non–GLP and two GLP–compliant studies conducted at the same laboratory. The *in vitro* screening genotoxicity tests were negative for Matrix–M1.

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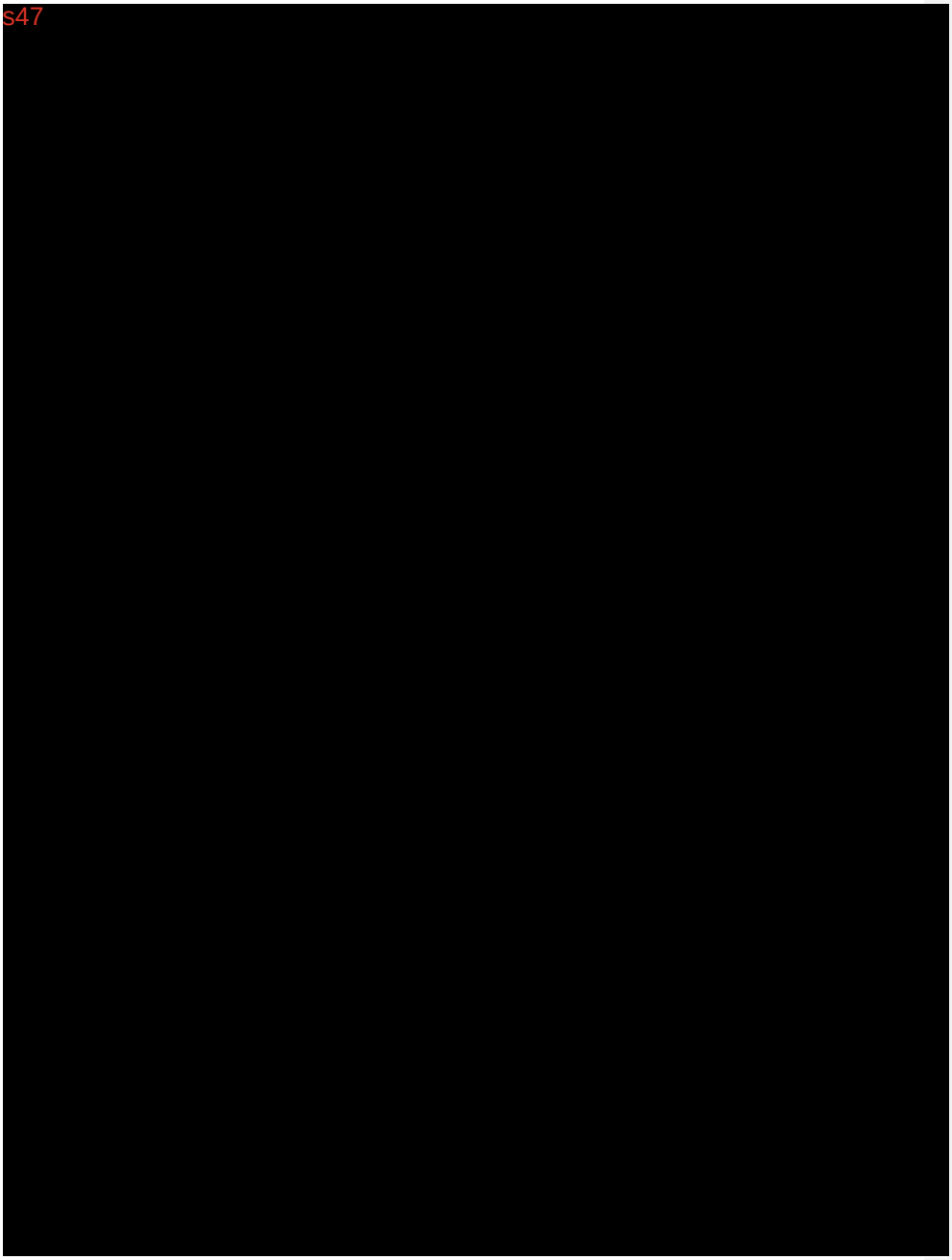

5. REPRODUCTIVE AND DEVELOPMENTAL STUDIES

Non-GLP pilot study with SARS-CoV-2 rS + Matrix-M1 was conducted first to confirm the immunogenicity of the intended dose and formulation in SD rats. A single GLP–compliant reproductive and developmental study in SD rats was conducted with SARS-CoV-2 rS + Matrix-M1 and Matrix-M1 only, which is evaluated below. The Sponsor has stated that "*no male fertility studies are planned given no adverse observations in male reproductive organs were observed in the GLP repeat-dose toxicology study*" (Module 2.4, Nonclinical overview, Section 2.4.4.5, Pg. 32).

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6. LOCAL TOLERANCE

Separate local tolerance studies were not submitted. Local tolerance was evaluated in the repeat-dose toxicity study with SARS-CoV-2 rS +100 µg/mL Matrix-M1 in rabbits and local tolerance of Matrix-M1 was assessed in repeat–dose toxicity studies with other vaccines in animals treated with the adjuvant, Matrix-M1 only (Section 3).

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Australian Government
Department of Health
Therapeutic Goods Administration

Nonclinical Evaluation Report

SARS-CoV-2 rS (NVX-CoV2373) [NUVAXOVID®]

Submission No: PM-2021-00623-1-2

Sponsor: Biocelect Pty Ltd

June 2021 – Interim report
October 2021 – Product information submission
December 2021 – Interim report (S31 response)
January 2022 – Final report

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New vaccine
Sponsor: Biocelect Pty Ltd
Generic name: **SARS-CoV-2 rS (NVX-CoV2373)**
Trade name: **NUVAXOVID®**
Dose form and strength: Solution for IM injection; 5 µg
Vaccine Type: Recombinant viral vaccine

Submission No: PM-2021-00623-1-2
Tox file No: E21-233938
TRIM reference: D21-2247953

Date authorised: 24 June 2021 — Interim report
01 October 2021 — Product Information submission
09 December 2021 — Interim report (S31 response)
03 January 2022— Final report

TABLE OF CONTENTS

SUMMARY

- Biocelect Pvt Ltd has applied for provisional registration of a new vaccine, SARS-CoV-2 rS (NVX-CoV2373) (NUVAXOVID®), a SARS-CoV-2 recombinant (r) spike (S) protein antigen (SARS-CoV-2 rS) with Matrix-M1 adjuvant. SARS-CoV-2 rS is proposed to be used for the prevention of mild, moderate, and severe disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proposed dosing regimen involves 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) is given on Days 0 and 21 intramuscularly (IM).

- The Sponsor has generally conducted adequate studies on pharmacology and toxicity of the vaccine and its adjuvant Matrix-M1 (novel excipient containing purified saponins extracted from *Quillaja saponaria*). All repeat-dose toxicity, genotoxicity and reproductive toxicity studies for the vaccine and adjuvant were performed under GLP conditions. No pharmacokinetic studies were conducted with the antigen or the adjuvant. One tissue distribution study with the adjuvant is planned.

- SARS-CoV-2 rS vaccine (i.e., SARS-CoV-2 rS antigen + Matrix-M1 adjuvant) was found to be immunogenic in nonclinical studies in mice, rats, hamsters, rabbits and non-human primates (NHP). SARS-CoV-2 rS vaccine induced both humoral (anti-S, hACE2 receptor binding blocking and virus neutralising antibodies) and cellular immune (Th-1 biased) response in mice and NHP.

- One or two boost immunisations ~10 months following primary immunisation with a different SARS-CoV-2 S protein variant (SA B.1.351 + Matrix-M1), induced strong humoral and cellular immune response against at least three SARS-CoV-2 S protein variants in baboons.

- s47 [redacted]

- The vaccine provided some protection from infection in mice, hamsters and primates when challenged after two immunisation doses, based on viral RNA and subgenomic RNA load and lung histopathology. The immunisation regimen in monkeys was identical to the proposed clinical immunisation regimen (5 µg SARS-CoV-2 rS +50 µg Matrix-M1, 2 IM doses, 21 days apart).

- Lung histopathological changes were less severe in challenged immunised primates compared to challenged controls. Primates do not show SARS-CoV-2 infection-related clinical signs and generally develop only mild lung pathology. There were no studies on protection of older animals from SARS-CoV-2 infection. *In vivo* primary pharmacology studies were of short term; two long term immunogenicity studies are still ongoing.

- No enhanced lung pathology was evident in immunised, virus challenged animals. Findings in a repeat-dose toxicity study with SARS-CoV-2 rS ± Matrix-M1 by the IM route in rabbits showed local reactions at the injection site and elevated serum levels of fibrinogen, C–Reactive protein and globulin in plasma. While no effects on draining lymph node and spleen were observed in the rabbit with SARS-CoV-2 rS ± Matrix-M1, hyperplasia, plasmacytosis and heterophil infiltrates in draining lymph node and/or spleen were observed in rats and rabbits treated with Matrix-M1 with or without an antigen. All the findings were related to immune response to the vaccine and adjuvant and fully or partially reversible a few weeks after the last treatment. Both the SARS-CoV-2 rS vaccine and the Matrix-M1 adjuvant alone were well tolerated.

- Matrix-M1 was negative in two *in vitro* genotoxicity tests (Ames test and chromosomal aberration test in Chinese Hamster Ovary cells). No *in vivo* genotoxicity study was performed. This is considered acceptable as it was negative in in vitro assays, and the saponin fractions are plant-derived and are approved food additives.

- In a combined reproductive and developmental toxicity study with SARS-CoV-2 rS + Matrix-M1, and Matrix-M1 alone female fertility, embryofetal development and postnatal development of offspring were unaffected.

CONCLUSIONS AND RECOMMENDATION

- SARS-CoV-2 rS + Matrix-M1 elicited both humoral and cellular immune responses to the spike (S) antigen in mice, hamsters and non-human primates and conferred some protection from SARS-CoV-2 infection.
    - Primary pharmacology studies investigating the potential long-term immunity following immunisation with SARS-CoV-2 rS + Matrix-M1 adjuvant vaccine in non-human primates are still ongoing. In baboons, one or two boost immunisations (21 days apart) – with a different SARS-CoV-2 antigen (beta variant) – 10 months following primary immunisation induced rapid and strong immune response against SARS-CoV-2 US-WA1, SA B1.351 and UK B.1.1.7 variants.
- Repeat–dose toxicity studies with the proposed vaccine in rabbits and Matrix-M1 in rats and rabbits raised no safety issues. Treatment–related findings were limited to immune response-related effects.
- SARS-CoV-2 rS + Matrix-M1 did not adversely affect female fertility, embryofetal development or postnatal development in rats. Pregnancy category B1 is considered appropriate.
- Matrix-M1 was not genotoxic.
- All safety studies were conducted with Discovery or EBSI batches. While mouse immunogenicity studies showed comparability between Discovery, SKBio, FDBU and EBSI batches, there are no immunogenicity and safety studies to demonstrated comparability between the commercial batches to be marketed in Australia and the nonclinical batches.
- There are no nonclinical objections to the provisional approval of this vaccine provided Module 3 data showed comparability between nonclinical and commercial batches and/or efficacy and safety have been adequately demonstrated by clinical data for the commercial batches.
- The ongoing immunogenicity studies and planned tissue distribution study should be provided for review once they are completed.
- The draft Product Information should be amended as directed on pages 17–19.

ASSESSMENT

Biocelect Pty Ltd has applied for provisional registration of a new COVID-19 vaccine (also known as NVX-CoV2373 or Novavax COVID-19 Vaccine) (Nuvaxovid®). The vaccine consists of a recombinant (r) spike (S) protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as SARS-CoV-2 rS, as the antigen and Matrix-M1 as the adjuvant. It is indicated for the active immunisation for the prevention of mild, moderate, and severe disease caused by SARS-CoV-2 in adults ≥18 years of age. The proposed dosing regimen is 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) given on Days 0 and 21 intramuscularly (IM).

General comments

SARS-CoV-2 rS vaccine is an adjuvanted recombinant full-length SARS-CoV-2 spike glycoprotein vaccine. This vaccine does not contain live virus.

Module 4 comprised of nonclinical studies with the clinical formulation and the adjuvant with other vaccine antigens. Reports of all completed studies have been provided. Two immunogenicity studies and one tissue distribution study are ongoing, and the absence of these studies do not preclude provisional approval of the vaccine.

The adjuvant, Matrix-M1 consists of purified saponin fractions, cholesterol, and phospholipid and is a new excipient. Since the saponin fractions were plant-derived, they consist of a number of structurally related saponins and the amount of each saponin component may vary between batches. The potential effect of the variation of each saponin component on Matrix-M1 safety and/or efficacy has been addressed by the Sponsor. Overall, the variability in saponins in the purified saponin fractions is not considered to considerably affect Matrix-M1 and the adjuvanted vaccine safety and efficacy (see Section 1.6).

Pharmacology

SARS-CoV-2 is a single-stranded RNA-enveloped virus. Its surface is covered by a large number of trimeric spike (SAR-CoV-2 S) glycoproteins (Figure 1A). SARS-CoV-2 S protein comprises two functional subunits responsible for binding to host cell receptors (S1) and for fusion of virus and host cell membranes (S2). Cleavage by furin-like proteases between S1 and S2 subunits has been shown to be essential for the S-protein mediated cell-cell fusion and viral infectivity (Örd *et al.,* 2020). The proposed SARS-CoV-2 rS vaccine is constructed from the full-length, wild-type SARS-CoV-2 S, where the *S* gene was modified by mutation of the furin cleavage site (Figure 1B) to make it resistant to furin-like protease cleavage.

In prefusion state, SARS-CoV-2 S protein alternates between “open” and “close” conformations (Ke *et al.,* 2020; Figure 1C). When in the “open” conformation, SARS-CoV-2 S protein receptor-binding domain (RBD) binds human angiotensin-converting enzyme 2 (hACE2) (Berger & Schaffitzel, 2020; Ke *et al.,* 2020). SARS-CoV-2 S protein RBD has been shown to be a target antigen for neutralising antibodies (Yuan *et al.,* 2020). In the proposed SARS-CoV-2 vaccine, two proline amino acid substitutions were inserted within the heptapeptide repeat 1 (HR1) domain (B) to stabilise SARS-CoV-2 S in a prefusion conformation; therefore, the proposed SARS-CoV-2 rS vaccine is expected to optimise presentation of SARS-CoV-2 S protein RBD neutralising epitopes.

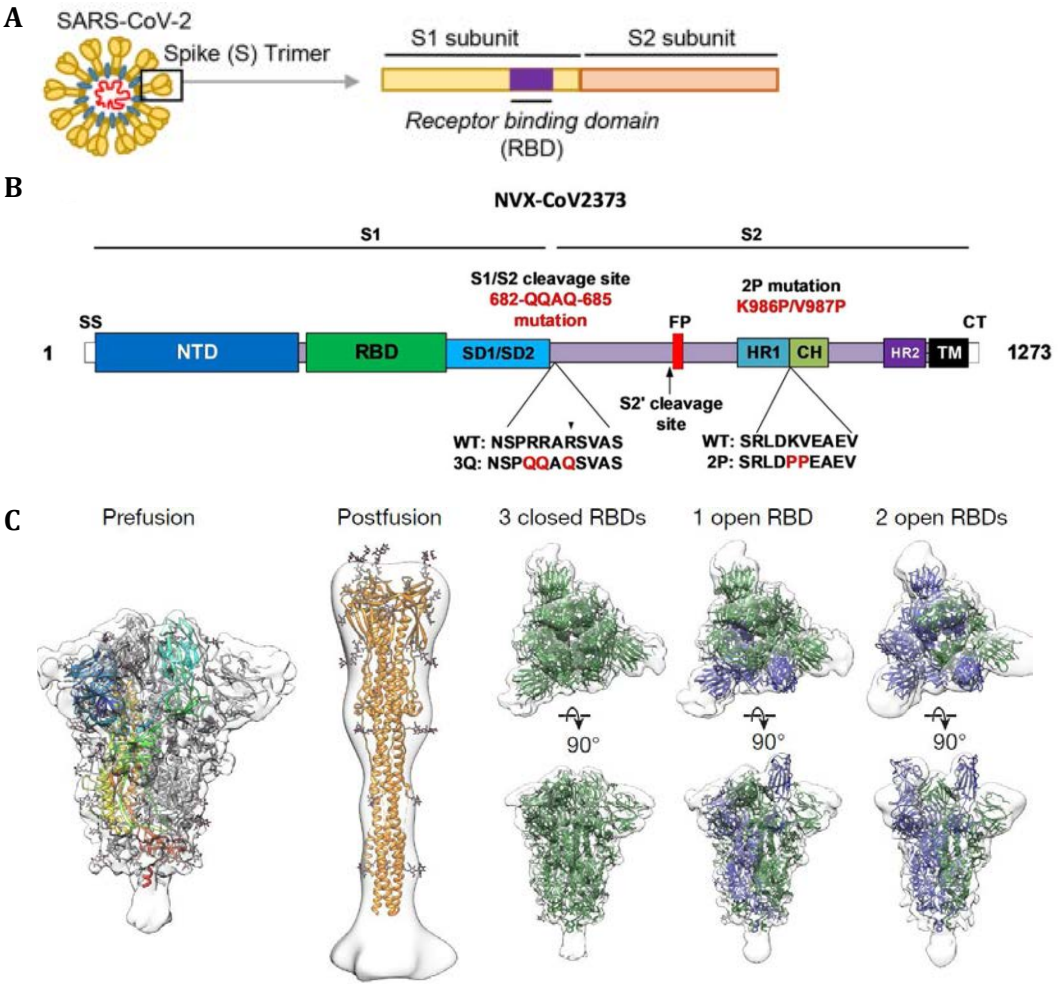

Figure 1. SARS-CoV-2 S structure and the spike protein construct (reproduced from Ke *et al.,* 2020; Tian *et al.,* 2020 & 2021)
CH = central helix; CT = cytoplasmic tail; FP = fusion peptide; HR = heptapeptide repeat; NTD = N-terminus domain; SD = subdomain; SS = signal sequence; TM = transmembrane domain

Primary pharmacology

Pharmacology studies were performed in mice (BALB/c), hamsters, baboons and macaques (cynomolgus and rhesus). Immunogenicity data was overall similar between laboratory species, i.e., high levels of anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibody titres and positive cellular responses in immunised animals. Prime–boost vaccine regimen increased protection against SARS-CoV-2 infection (shown by decreased viral load). Matrix-M1 adjuvant significantly increased vaccine immunogenicity. A Th1-biased immune response was observed in mice, baboons and macaques. No evidence of vaccine-elicited disease enhancement were observed in any of the protection studies. There were no studies on protection in older animals from SARS-CoV-2 infection or lon- term protection following immunisation. The proposed clinical dose SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose), immunisation interval (Days 0 and 21) and route of administration (IM) were studied in baboons and macaques.

Matrix-M1 mechanism of action

The adjuvant, Matrix-M1 is composed of Matrix-A (85%) and Matrix–C (15%), which are ~40 nm nanoparticles of saponin Fraction–A and –C, respectively, extracted from the tree Quillaja saponaria Molina, cholesterol and phospholipid. s47 [redacted]

s47 [redacted]

Immunogenicity

SARS-CoV-2 rS + Matrix-M1 vaccine was found to be immunogenic in mice, rats, hamsters, rabbits, and non-human primates (NHP - baboons, cynomolgus and rhesus macaques). The presence of Matrix-M1 adjuvant in SARS-CoV-2 rS vaccine increased its immunogenic response in mice or baboons *cf.* SARS-CoV-2 rS alone or vaccines + other adjuvant. A booster dose with Matrix-M1 adjuvant 21 days after the first dose markedly increased the humoral immune response (anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibodies) in mice and NHP. There was high correlation between anti-S, hACE2 receptor inhibiting and SARS-CoV-2 neutralising antibodies in multiple animal species including NHP.

s47 [redacted] Altogether, this indicates that SARS-CoV-2 rS + Matrix-M1 induce predominantly a Th1 driven immune response.

Similar findings were observed in NHP. s47 [redacted]

Overall, immunisation with SARS-CoV-2 rS + Matrix-M1 induced both humoral and cellular immune responses. The immune responses were Th1-biased. Two doses with a booster dose of 3-4 weeks after the first dose and the antigen dose of 5 µg + 50 µg Matrix-M1 as the adjuvant appear to be the optimal immunisation regimen. Increasing the antigen dose to 25 µg did not significantly increase immune responses. s47 [redacted]. A single boost immunisation, 10 months following primary immunisation induced strong and anamnestic antibody and cellular response.

SARS-CoV-2 rS + Matrix-M1 adjuvant also elicited immune responses in hamsters (anti-S, hACE2 receptor inhibiting and neutralising antibodies), rabbits (anti-S IgG) and rats (anti-S IgG) as investigated in primary pharmacology protection studies, repeat-dose toxicity studies, reproductive and developmental studies, respectively.

Immunogenicity comparison of drug substance (antigen) and drug product batches

Several SARS-CoV-2 rS drug substance (DS) and drug product (DP) produced by different manufacturers (Novavax [Discovery], Emergent BioSolutions, FUJIFILM Diosynth Biotechnologies, PAR Pharmaceuticals, and SK Bioscience), at different manufacturing scale with various purity and particle size were tested to evaluate their immunogenic potential in mice. All animals were immunised with two doses of SARS-CoV-2 rS + Matrix-M1 IM, 14 days apart (*cf.* 21 days apart for the clinical immunisation regimen). The Matrix-M1 batches tested were manufactured by s47 [redacted] The SARS-CoV-2 rS s47 [redacted] and were mixed with s47 [redacted]

Overall, all batches tested induced an immunogenic response (measured by anti-S and hACE2 receptor inhibiting antibody titres up to 28 days post initial immunisation). s47 [redacted], SARS-CoV-2 rs s47 [redacted] did not significantly affect the immunogenicity of the vaccine. However, it should be noted that the following parameters/variables have not been tested:

- The long-term immunogenic response;
- The effect of SARS-CoV-2 rS batch variability on cell-mediated immune response;

- The proposed clinical dose (5 µg) and dosing interval (3 weeks);
- Pharmacokinetic and safety profile of the vaccine particle size;
- Most importantly, commercial batches manufactured at s47

Protection against infection

SARS-CoV-2 rS + Matrix-M1 provided protection against SARS-CoV-2 challenge in mice (transiently transfected with hACE2), hamsters and macaques (cynomolgus and rhesus) after two immunisation doses.

In challenged mice immunised with a single dose of s47 a dose-dependent reduction in lung virus titre was observed. No viral load was detected in the lungs of animals immunised with the highest dose of adjuvanted vaccine.

s47

s47

No clinical signs were observed in challenged, unimmunised cynomolgus macaques which is consistent with other studies in SARS-CoV-2-infected NHP (Muñoz-Fontela et al. 2020). s47

s47

The predominant Th1-biased response observed in mice and primates suggests low risk of antibody-dependent enhancement (ADE) and vaccine-associated enhanced respiratory disease (VAERD) (for review see Munoz *et al.,* 2021). In addition, no enhanced lung pathology was evident in immunised, virus challenged animals.

The pharmacology studies indicated that SARS-CoV-2 rS + Matrix-M1 induces humoral (measured by anti-S IgG, hACE2 receptor inhibiting antibodies and virus-neutralising antibodies) and cellular (characterised by a predominant $CD4^+$ Th1 T-cell response) immune responses in mice and NHP. The vaccine protected mice, hamsters and NHP from infection when challenged s47 after the 2nd vaccine dose, respectively. Only the vaccine doses given to primates were identical to the proposed clinical dosing regimen. There were no studies on protection of older animals from SARS-CoV-2 infection. Pharmacology studies on the duration of protection after immunisation are still ongoing. s47 According to the EMA evaluation, the rhesus macaque study will cover homologous protection against the WA-1 isolate as well as heterologous protection against the antigenically divergent Brazilian isolate, and the baboon study will include immunogenicity data following boosting with an updated immunogen based on the South African virus variant. These studies will be reviewed once the study reports are available.

Is the vaccine effective against all variant SARS-CoV-2 viruses?

During the course of the pandemic, mutations have arisen in SARS-CoV-2 S protein that has become dominant amongst viruses sequenced from patient samples. It should be noted that SARS-CoV-2 rS + Matrix-M1 vaccine induced the production of wild-type virus neutralising antibodies. No nonclinical data on the efficacy against SARS-CoV-2 variants were provided.

A published study showed that serum samples from recipients of NVX-CoV2373 neutralised the B.1.1.7 variant, albeit at moderately reduced levels (~2-fold) (Shen *et al.,* 2021).

Safety pharmacology

Limited safety pharmacology parameters e.g. body temperature were investigated in the repeat-dose toxicity studies, in accordance with the WHO guideline on nonclinical evaluation of vaccines (2005)[1].

Pharmacokinetics

No pharmacokinetic studies were conducted. No pharmacokinetic studies are generally required for vaccine antigens in accordance with the WHO guideline on nonclinical evaluation of vaccines (2005). However, tissue distribution of adjuvants may be of value as recommended by the WHO guidelines on the nonclinical evaluation of vaccine adjuvants (2013)[2] and EMA guideline on adjuvants in vaccines for human use (2005)[3].

s47

Toxicity

Acute toxicity

No single-dose toxicity studies were performed with the SARS-CoV-2 rS and/or Matrix-M1 adjuvant. This is acceptable, with relevant information on acute toxicity available from repeat-dose toxicity studies instead, which are discussed below.

[1] WHO guidelines on nonclinical evaluation of vaccines (2005)
[2] WHO guidelines on the nonclinical evaluation of vaccine adjuvants (2013)
[3] Guideline on adjuvants in vaccines for human use (2005)

Repeat-dose toxicity

A 36–day GLP compliant repeat–dose toxicity study (Study 2088-20035) was conducted in rabbits using the IM route of administration with the clinical candidate vaccine, SARS-CoV-2 rS ± Matrix-M1.

s47 [redacted]

The dosing interval is considered adequate given that high antibody titres were detected after booster doses. Use of a single species (rabbits) is consistent with the relevant guidelines and demonstration of good immunogenicity supports the use of this species as an appropriate animal model for the toxicity study. Adequate number of animals were used in the study (10/sex/treatment group with 5/sex sacrificed after 3 doses and 5/sex after 4 doses, plus 5/sex/group for recovery observations).

As toxicokinetic data for the adjuvant were not obtained in the repeat–dose toxicity studies, animal to human exposure comparisons have been made based on body surface area adjusted doses (Table I). In the pivotal repeat–dose toxicity study in rabbits, Matrix-M1 (plus SARS-CoV-2 rS; no adjuvant only group) was s47 [redacted]

s47 [redacted]

Major toxicities

In the repeat-dose toxicity study with IM injections of 50 µg SARS-CoV-2 rS (± 50 µg Matrix-M1), treatment–related findings were limited to inflammation at the injection site with increased subcutaneous (minimal to mild) cellular infiltration, minimal oedema/erythema and myofibre degeneration. At the end of the 21-day recovery period, the inflammation changes partially recovered. Overall, 3 IM injections of SARS-CoV-2 rS (± Matrix-M1) given 7 days apart were locally and systemically well tolerated. Other treatment-related findings included elevated levels of fibrinogen, C–reactive protein and globulin, which lowered during the recovery phase. No effects on spleen and only mild effect on draining lymph nodes (like hyperplasia and inflammation, reported in other studies with Matrix-M1 with or without an antigen) were observed in this study. Mild histiocytic heterophil infiltrate of the right iliac lymph node was observed in only 1 female receiving SARS-CoV-2 rS + Matrix-M1. Serology data demonstrated detection of specific antibodies, with the Matrix-M1 adjuvant significantly enhancing the anti-S IgG response in rabbits.

Other studies including an adjuvant only treatment group demonstrated similar treatment–related findings of acute inflammation (subcutaneous [minimal to mild] cellular infiltration), which fully or partially reversed during the recovery period and elevated serum levels of fibrinogen, C–reactive protein and globulin, which lowered during the recovery phase. s47 [redacted]

Genotoxicity

No genotoxicity studies were conducted for SARS-CoV-2 rS (antigen) or the vaccine formulation. This is in line with relevant guidelines for vaccines.

Matrix-M1 as a novel adjuvant was tested in two non-GLP *in vitro* genotoxicity pilot–studies s47 [redacted] and two GLP-compliant *in vitro* genotoxicity studies s47 [redacted] The assays were adequately validated and returned negative results.

No *in vivo* genotoxicity study was provided for the novel adjuvant, Matrix-M1. While the WHO guidelines on the nonclinical evaluation of vaccine adjuvants recommend a standard battery of genotoxicity studies for novel adjuvants that are new chemical entities[2], the Sponsor has not planned to conduct an *in vivo* genotoxicity study as Matrix-M1 adjuvant was non-mutagenic in the GLP *in vitro* genotoxicity studies. The Sponsor indicated that both the EMA and FDA had agreed to the Sponsor's approach on genotoxicity testing of Matrix-M1, and also noted that Quillaja saponins are used as food additives with an acceptable daily intake (ADI) of 1 mg/kg/day (JECFA, for semi-purified extract) or 3 mg/kg (EFSA)[4]. However, there are no data on oral bioavailability of Quillaja saponins, and Quillaja saponins are expected to have very low oral bioavailability based on studies with other saponins. Nonetheless, the saponins in Matrix-M1 are plant-derived and Quillaja saponins have been used as a

[4] EFSA Panel on Food Additives and Flavourings. Re-evaluation of Quillaia extract (E999) as a food additive and safety of the proposed extension of use. EFSA J. 2019 Mar 6; 17(3):e05622. doi.org/10.2903/j.efsa.2019.5622.

food additive for decades. Based on all of the above, the absence of *in vivo* genotoxicity studies for Matrix-M1 is considered acceptable.

Carcinogenicity

Carcinogenicity studies were not conducted. This is acceptable based on its duration of use. The novel adjuvant, Matrix-M1 is not expected to be carcinogenic based on the low exposure, duration of exposure, and the negative results in two *in vitro* genotoxicity assays.

Reproductive toxicity

As SARS-CoV-2 rS vaccine is proposed to be used for the active immunisation of individuals from the age of 18 years, there is potential for administration of the vaccine to pregnant women.

A non-GLP pilot study with SARS-CoV-2 rS (10 µg) + Matrix-M1 (20 µg) was conducted first to confirm the immunogenicity of the intended dose and formulation in SD rats. SARS-CoV-2 rS + Matrix M1 was well tolerated and elicited an immune response in rats following 2 IM injections on Days 1 and 15.

A GLP–compliant, combined reproductive and developmental toxicity study with SARS-CoV-2 rS + Matrix-M1, and Matrix-M1 alone in rats showed no test item–related adverse effects on female fertility, and embryofetal and postnatal development. SARS-CoV-2 rS + Matrix M1 elicited an immune response in rats following 4 IM injections. s47 [redacted] This is acceptable given the absence of effects on male reproductive organs in rats and rabbits receiving up to 4 doses of Matrix-M1-adjuvanted vaccines or adjuvant alone, and the proposed vaccine would be administered to humans infrequently. Based on the study, this vaccine is not consider to pose a risk for use in pregnant women.

Pregnancy classification

The Sponsor has proposed a pregnancy Category B1. The Pregnancy Category B1 is considered appropriate for this product as the reproductive toxicity study in female rats revealed no adverse effects on embryofetal development or postnatal development of offspring.

Local tolerance

No separate local tolerance studies were submitted. Local tolerance was assessed in the repeat dose toxicity study with SARS-CoV-2 rS (NVX-CoV2373) and studies with Matrix-M1. Local reactions observed in the repeat-dose toxicity studies performed with SARS-CoV-2 rS + Matrix-M1 or Matrix-M1 in rats or rabbits were limited to minimal to mild inflammation at the injection sites, and extending to the sciatic nerve and were fully or partially reversible (see *Repeat-dose toxicity* above).

Adjuvant – Matrix-M1

Matrix-M1 adjuvant is derived from fractionated *Quillaja saponins* plus phosphatidylcholine, and cholesterol formulated into ~40 nm cage-like structures. Matrix-M1 is a novel adjuvant, and nonclinical toxicity study requirements for a new chemical entity (NCE) are applicable.

GLP–compliant repeat-dose toxicology studies in rats and rabbits with the Matrix-M1 adjuvant were submitted, along with a combined reproductive and developmental toxicity study (with a Matrix-M1 only treatment group) and two *in vitro* genotoxicity studies. Toxicological effects of Matrix–M1 in the submitted studies have been evaluated and discussed in the relevant sections above. Safety of the novel adjuvant, Matrix-M1 has been adequately assessed in animal studies. The planned tissue distribution study will provide further information on mechanisms of action and target tissues of potential toxicity.

Paediatric use

SARS-CoV-2 rS (NVX-CoV2373) is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for SASR-CoV-2 rS with Matrix-M1 adjuvant detailed in the Sponsor's draft European Union Risk Management Plan (Part II: Module SII) are in general concordance with those of the Nonclinical Evaluator.

PRODUCT INFORMATION

The following comments refer to the draft Product Information document (1.3.1.2 NUVAXOVID product information v0.4 - tracked 29 Dec 21; TRIM reference D21-3479674). Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

With no relevant nonclinical studies available, the proposed statement is considered to be acceptable from a nonclinical perspective.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

It should be mentioned that the reproductive and developmental toxicity study in rats did not evaluate effects on male fertility. Additionally, the relative exposure for Matrix-M1 adjuvant should be corrected. The preferred Australian spelling of *fetus* should be used (the additional *'o'* having no etymological basis[5]). The following text is recommended:

> "Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
>
> A developmental and reproductive toxicity study was performed in female rats administered four intramuscular doses (2 prior to mating; 2 during gestation) of 5 micrograms SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 micrograms on a weight-adjusted basis) with 10 micrograms Matrix-M adjuvant (approximately s47 -fold excess relative to the human dose of 50 micrograms on a s47 -adjusted basis). No vaccine-related adverse effects on s47 fertility, pregnancy/lactation, or development of the s47 and offspring through post-natal Day 21 were observed. s47

Use in pregnancy

The sponsor proposes Pregnancy Category B1 and the following statement:

> "Proposed pregnancy category – B1.
>
> There is limited experience with use of NUVAXOVID in pregnant women.
>
> Animal studies did not show vaccine related adverse effects on embryofetal development (see Effects on fertility).
>
> Administration of NUVAXOVID in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus."

The proposed Pregnancy Category B1 is considered appropriate for this product as no embryofetal effects have been noted in a combined reproductive and development study in rats. The preferred Australian spelling of fetus should be used. The statement regarding the proposed pregnancy

[5] Macquarie Dictionary usage note: The etymology of this word is from a Latin form *fetus*. The spelling *foetus*, probably based on false analogy with words such as *oedema* and *oestrogen*, was widely used, although health authorities increasingly recommend the spellings *fetus* and *fetal*.

category should be removed since it is already noted in the heading. The following changes are recommended:

s47

There is limited experience with use of NUVAXOVID in pregnant women.

s47 did not show vaccine related adverse effects on embryofetal development (see Effects on fertility).

Administration of NUVAXOVID in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and s47

Use in lactation

The proposed text is acceptable with a minor editorial change. The preferred Australian spelling of fetus should be used. Thus:

"It is unknown whether NUVAXOVID is excreted in human milk.

Administration of NUVAXOVID in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and s47

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Statements on the mechanism of action are supported by nonclinical data. Minor editorial changes are suggested. Thus:

"NUVAXOVID is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The 2 vaccine components elicit B- and T-cell immune responses to the S protein, including s47, which protect against COVID-19."

5.3 PRECLINICAL SAFETY DATA

Statements regarding general and reproductive toxicity should be deleted from this section. Thus:

s47

Genotoxicity

Information on the genotoxicity assays conducted should be provided and "*In vitro*" should be italicised. Thus:

s47 genotoxicity studies s47 were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic."

Carcinogenicity

The proposed statement noting the absence of carcinogenicity studies is considered acceptable.

> "Carcinogenicity studies were not performed. The components of the vaccine are not expected to have carcinogenic potential."

MAIN BODY OF REPORT

1. INTRODUCTION

1.1. BACKGROUND

Biocelect Pty Ltd has applied for provisional registration of a new COVID-19 vaccine (also known as NVX-CoV2373 or Novavax COVID-19 Vaccine) (NUVAXOVID®). The vaccine consists of a recombinant (r) spike (S) protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as SARS-CoV-2 rS, as the antigen and Matrix-M1 as the adjuvant. It is indicated for the active immunisation for the prevention of mild, moderate, and severe disease caused by SARS-CoV-2 in adults ≥18 years of age. The proposed dosing regimen is 2 doses (0.5 mL/dose) of SARS-CoV-2 rS (5 µg per dose) with Matrix-M1 adjuvant (50 µg per dose) given on Days 0 and 21 intramuscularly (IM).

1.2. RELATED VACCINES

SARS-CoV-2 rS (NVX-CoV2373) vaccine is the first SARS-CoV-2 recombinant spike protein adjuvanted vaccine to be proposed for registration in Australia. There are currently two other vaccines registered for COVID-19, ChAdOx1-S COVID-19 Vaccine (COVID-19 VACCINE ASTRAZENECA®) and BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY™).

1.3. RECOMBINANT SARS-COV-2 SPIKE PROTEIN CONSTRUCT

SARS-CoV-2 recombinant (r) spike (S) protein (SARS-CoV-2 rS) vaccine is constructed from the full-length, wild-type SARS-CoV-2 spike protein gene sequence (GenBank MN908947; nucleotides 21563–25384). It was codon optimised to improve expression in *Spodoptera frugiperda* (Sf9) insect cells. The construct was modified at the S1/S2 cleavage site (RRAR to QQAQ [3Q]; see below) to make it protease resistant. Two proline substitutions were inserted in the S2 fusion machinery within the heptad repeat 1 domain (HR1; at residues K986 and V987 [2P]) to enhance S2 stability in a prefusion conformation (Bangaru *et al.,* 2020; Wrapp *et al.,* 2020). The double mutant 3Q-2P SARS-CoV-2 rS transgene was cloned into the baculovirus[6] transfer vector. Recombinant baculovirus constructs were then transfected into Sf9 insect cells.

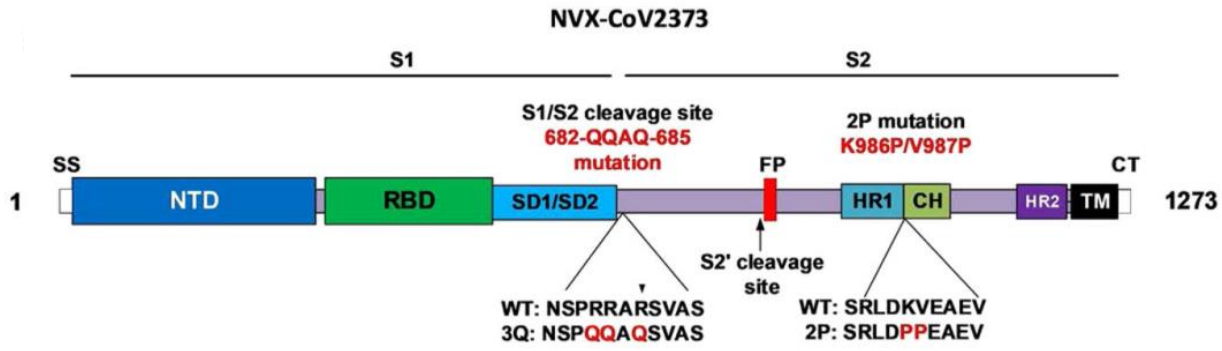

Figure 1.1. Full-length optimised spike protein construct (reproduced from Tian *et al.,* 2021)

[6] an insect enveloped virus; highly infectious to cultured insect cells and non-pathogenic to humans

1.4. SARS-CoV-2 rS VACCINE ADJUVANT

Isolated and purified SARS-CoV-2 rS protein trimers were adjuvanted with the saponin-based Matrix-M1 adjuvant. The Sponsor indicated (TRIM reference D20-3630324) that the adjuvant "*is derived from fractionated Quillaja saponins, phosphotidyl choline, and cholesterol formulated into ~40 nm cage-like structures. Quillaja saponins are extracted from the bark of the tree Quillaja saponaria Molina, in a multi-step process before being mixed with cholesterol and phospholipids using a proprietary method to create the Matrix particles. Matrix-M1 is formulated in phosphate buffered saline (PBS) to create the bulk adjuvant.*"

1.5. PRODUCT FORMULATION

SARS-CoV-2 rS (NVX-CoV2373) supplied as a preservative free liquid formulation for IM administration. It is available as vials containing 10 doses of 0.5 mL/dose of vaccine. The vaccine contains Matrix-M1 as adjuvant, and SARS-CoV-2 rS antigen (laboratory code BV2373); produced by recombinant technology from Sf9 cells (see Section 1.3). Quantities of antigens, adjuvant and excipients are outlined below in Table 1.1.

Table 1.1. Product formulation

Ingredient	Function	s47 [redacted]
SARS-CoV-2 rS (NVX-CoV2373)	Active ingredient	
Matrix-M1*	Adjuvant	
Disodium hydrogen phosphate heptahydrate	NA	
Sodium dihydrogen phosphate monohydrate	NA	
Sodium chloride	NA	
Polysorbate 80	Stabilizer	
Sodium hydroxide	pH	
Hydrochloric acid	pH	
Water for injection	Solvent	

* = Matrix-A and Matrix-C components are mixed to form Matrix-M1 adjuvant, just prior to mixing with DS. Matrix-M1 is a novel excipient
NA = not available

1.6. MATRIX-M1 ADJUVANT

Martix-M1 adjuvant is a novel excipient, derived from fractionated Quillaja saponins, phosphatidylcholine, and cholesterol formulated into s47 nm diameter cage-like structures (TRIM reference D20-3630324).

1.6.1. Saponins structure and Matrix-M1 adjuvant formulation

In its email to TGA names dated 14 January 2021 (TRIM reference D21-2056500) the Sponsor provided the following information: "*SARS-CoV-2 rS vaccine includes an adjuvant (Matrix-M1) which is manufactured using fractionated Quillaja saponins derived from the tree Quillaja saponaria Molina. The Fraction-A and Fraction-C saponins are produced from saponin raw material… The saponin fractions consist of the structurally related saponins* s47 [redacted]

s47 [redacted]

As indicated above, Fraction-A and Fraction-C "*consist of a number of structurally related saponin components*". The identification and characterisation of the saponin residues in Fraction-A and Fraction-C was performed by LC/ESI-MS/MS. The study showed that *"the fractions contain a few major saponins and a number of minor saponins.* s47 [redacted] (AAN application, TRIM reference D21-2104584).

s47 [redacted]

The Sponsor also indicated that *"the purified Fraction A and Fraction C are then formulated to Matrix-A and Matrix-C which are identified by individual company codes"* 10-100-402 and 10-010-202, respectively (AAN application, TRIM reference D21-2056500).

Matrix-A and Matrix-C are nanoparticles made of purified saponin fractions, cholesterol, and phospholipid (TRIM references D20-3630324 & D20-3665265). The Sponsor specified that the drug product (DP) is formulated by mixing Matrix-A (85%) and Matrix-C (15%) into Matrix-M1 and adding the antigen (TRIM reference D20-3665265). s47 [redacted]; TRIM reference D20-3630324).

There is no information on the amount of cholesterol and phospholipid in Matrix-M1. This will be included after the submission of Module 3 data. Since both cholesterol and phospholipid are common excipients in parenteral formulations, they are not considered to be of safety concern.

1.6.2. Saponins structure-activity relationship

According to the published literature, saponin-based adjuvants have been studied for use in the development of new vaccines (Didierlaurent *et al.,* 2014; Wilson *et al.,* 2012). They have been shown to activate cytokine production (IFNs and ILs). Adjuvanticity of saponins is due to the presence of different residues to the main triterpenoid (C30) structure (see Figure 1.2). Several published papers have proven a direct relationship between the saponins structure and activity (for review see Sharma *et al.,* 2020; Rajput *et al.,* 2007). The presence of

- aldehyde group plays a "*role in maintaining the integrity and strength of Th1 response. Axial aldehyde shifts the immune system toward the stimulation of humoral immune responses, whereas equatorial aldehyde produces cell-mediated immune responses.*" (Sharma *et al.,* 2020)
- acyl groups enhance the activation of cytotoxic T lymphocytes (CTL). "*Deacylation of saponins… shows reduced antibody production and Th1 response compared to the acylated saponin, suggesting that the acyl residues are important for the activation of CTL-mediated immune response.*" (Sharma *et al.,* 2020)
- sugar chains are involved in the initiation of the immune response and also have an haemolytic effect (Sharma *et al.,* 2020). It has been demonstrated that "*the balance between these sapogenin [aglycone] (hydrophobic) and sugar chain (hydrophilic) properties is important for maintaining the adjuvanticity of saponins.*"

Saponin molecules can cause haemolysis of red blood cells; which is presumably due to their affinity for cell membranes components such as cholesterol and phospholipids (for review see Lorent *et al.,* 2014). In their review, Sharma *et al.* (2020) indicated that the *"hemolytic activity of the saponin molecules is mainly due to the presence of saccharide side chain and the acyl residues in the aglycone*". However, the haemolytic activity of saponins does not appear to be related with their adjuvanticity (Sharma *et al.,* 2020; Rajput *et al.,* 2007). Rönnberg *et al.* (1995) demonstrated that complexing *Quillaja saponaria* Molina saponin with cholesterol and phospholipid molecules to form a cage-like structure adjuvant (ISCOM) reduced the haemolytic activity associated with saponins. Therefore, the haemolytic activity of saponin contained in the proposed SARS-CoV-2 rS vaccine is not considered to be a potential safety concern when complexed with cholesterol and phospholipids.

However, based on the above it is considered that the different saponins present in Matrix-M1 adjuvant can affect the DP pharmacokinetics, immunogenicity and safety. The data provided in Module 4 is not sufficient to accurately establish the safety and/or efficacy of Matrix-M1 adjuvant in the DP. The Sponsor was requested to address items 1–4 below. A response to the S31 request (see below) was received on 31st May 2021.

1. Does the Sponsor have a strategy in place to monitor the relative amount of each saponin component contained in Fraction-A/Matrix-A, Fraction-C/Matrix-C or Matrix M1?

The Sponsor specified that "*a conservative approach for selection* [of bark extract lots] *is maintained, choosing materials that are similar to those already used to avoid non-common elements.*" (see Table 3-2). The Sponsor indicated that Fraction-A and Fraction-C saponins are isolated from *"Highly purified bark extract from Quillaja saponaria* Molina*"* by HLPC*. …*

s47

The purity of Fraction-A and Fraction-C saponins is tested by HPLC and batch release testing for three batches of Fraction-A and Fraction-C demonstrated comparability.

It should be noted that the initial characterisation of saponin fractions demonstrated that Fraction-A has poor to no adjuvanticity and its haemolytic potential is low; while Fraction-C has potent adjuvant activity and medium haemolytic potential. Both fractions were shown to contain saponins with good matrix-forming ability (see Table 4-1).

s47

2. Please provide composition details of each Matrix-M1 batch (including the concentration of each saponin component) used in nonclinical and clinical studies.

The Sponsor indicated that the saponin content in Matrix-A and Matrix-C is characterised at the Fraction-A and Fraction-C level. "*The saponin components in the Fraction-A and Fraction-C materials are governed by the fractionation process… The target composition of Matrix-A and Matrix-C in Matrix-M1 is 85:15 (w:w* [ratio 5.67]*) as measured by the Fraction-A and Fraction-C concentrations, respectively.*"

s47

3. Please provide information on any differences in the manufacture of Fraction-A/Matrix-A, Fraction-C/Matrix-C and Matrix M1 batches used in the nonclinical studies and clinical studies (including batches for marketing).

The Sponsor indicated that "*There are no differences between the manufacture of Fraction-A/Matrix-A, Fraction-C/Matrix-C, and Matrix-M1 batches used in the nonclinical studies and clinical studies in relation to formulation or composition, nor is there any plan to change the formulation or composition with respect to batches being manufactured for marketing.*"

4. Please comment on the impact of saponin components variations in Matrix-M1 on the safety and efficacy of Matrix-M1 and the vaccine.

The Sponsor pointed out that several batches of Matrix-M1 were used in *in vivo* primary pharmacology studies and repeat-dose toxicity studies. All tested batches produced strong adjuvant-related immune responses. The Sponsor indicated that no adjuvant-related changes in safety profile was observed in these studies and that the adjuvant was overall well tolerated. Similarly, Matrix-M1 based vaccines "*are generally well tolerated and have an acceptable safety profile*" in clinical studies. The Sponsor considers that because the "*safety (reactogenicity) and immune responses have been consistent across clinical trials … which led to demonstration of vaccine efficacy of 89.7% in a Phase 3 trial … Thus, the safety and efficacy obtained in nonclinical and clinical studies for SARS-CoV-2 rS with Matrix-M1 adjuvant is expected to be representative of the minor variations in saponin components (within specifications) that will be used in the commercial setting and no impact on the safety or efficacy have been observed within this variation.*"

Conclusion:

The Nonclinical Evaluator notes that although the "*purity of the fractions has been increased*", the "*diversity and content of the core fractions*" has been maintained. Based on the Sponsor's S31 response, it appears that the exact component content of Fraction-A and Fraction-C saponins will not be determined. Initial characterisation of fractions of saponins showed that Fraction-A has poor to no adjuvanticity with a low haemolytic potential, while Fraction-C has potent adjuvant activity and medium haemolytic potential. The Nonclinical evaluator considers that the variation in the amount of Matrix-C present in Matrix-M1 is more likely to impact the safety and efficacy of the adjuvanted vaccine. s47 [redacted] The variability in Matrix-C concentration in the DP is considered marginal and major changes in Matrix-M1 safety and efficacy are not expected.

1.7. BATCHES USED IN MODULE 4 STUDIES

The tables below list the antigen (SARS-CoV-2 rS – BV2373) and Matrix-M1 adjuvant batches (Table 1.4 and Table 1.5) as well as Matrix-M1 formulation (Table 1.6) used in the nonclinical studies.

s47 [redacted]

s47

s47

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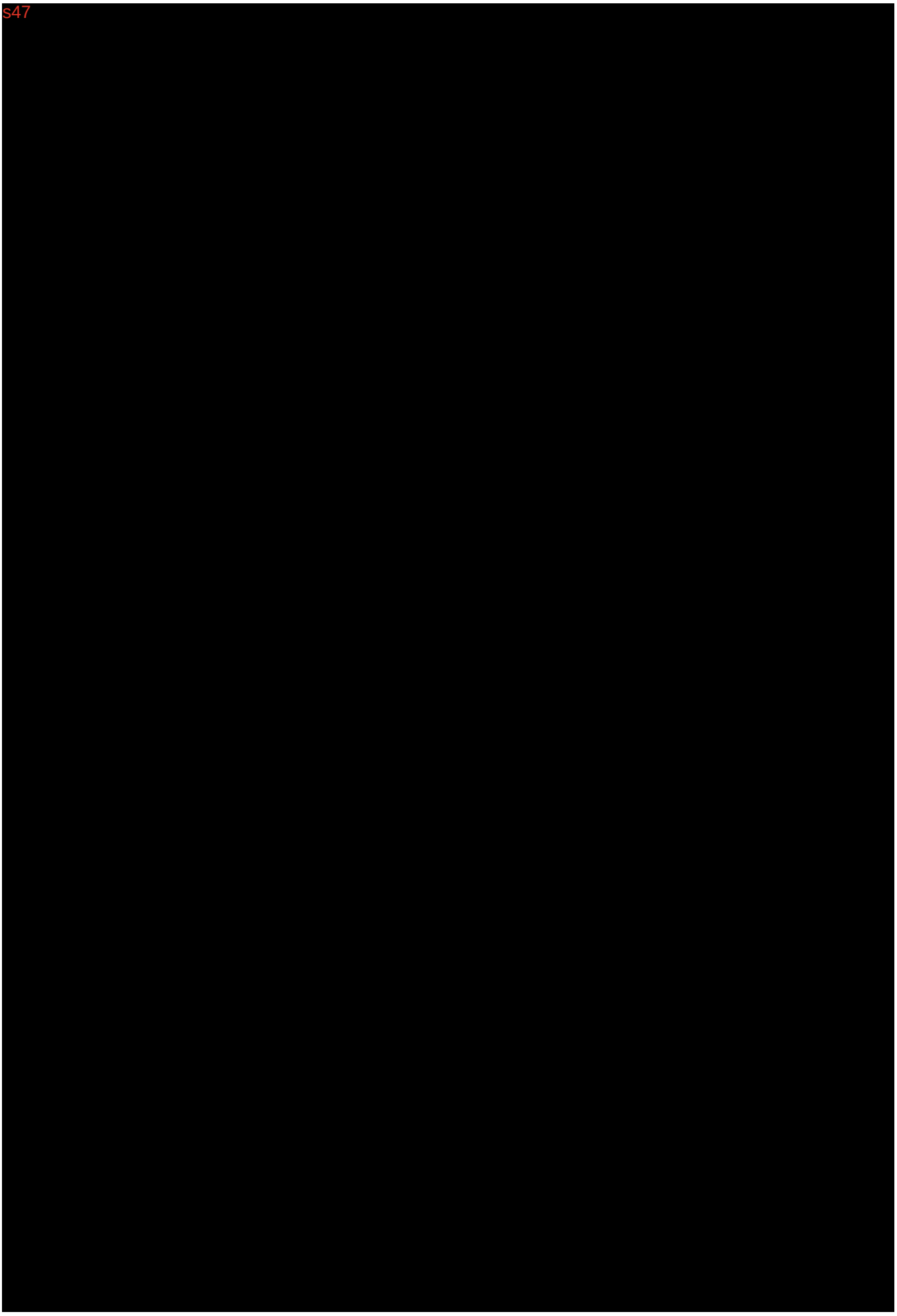

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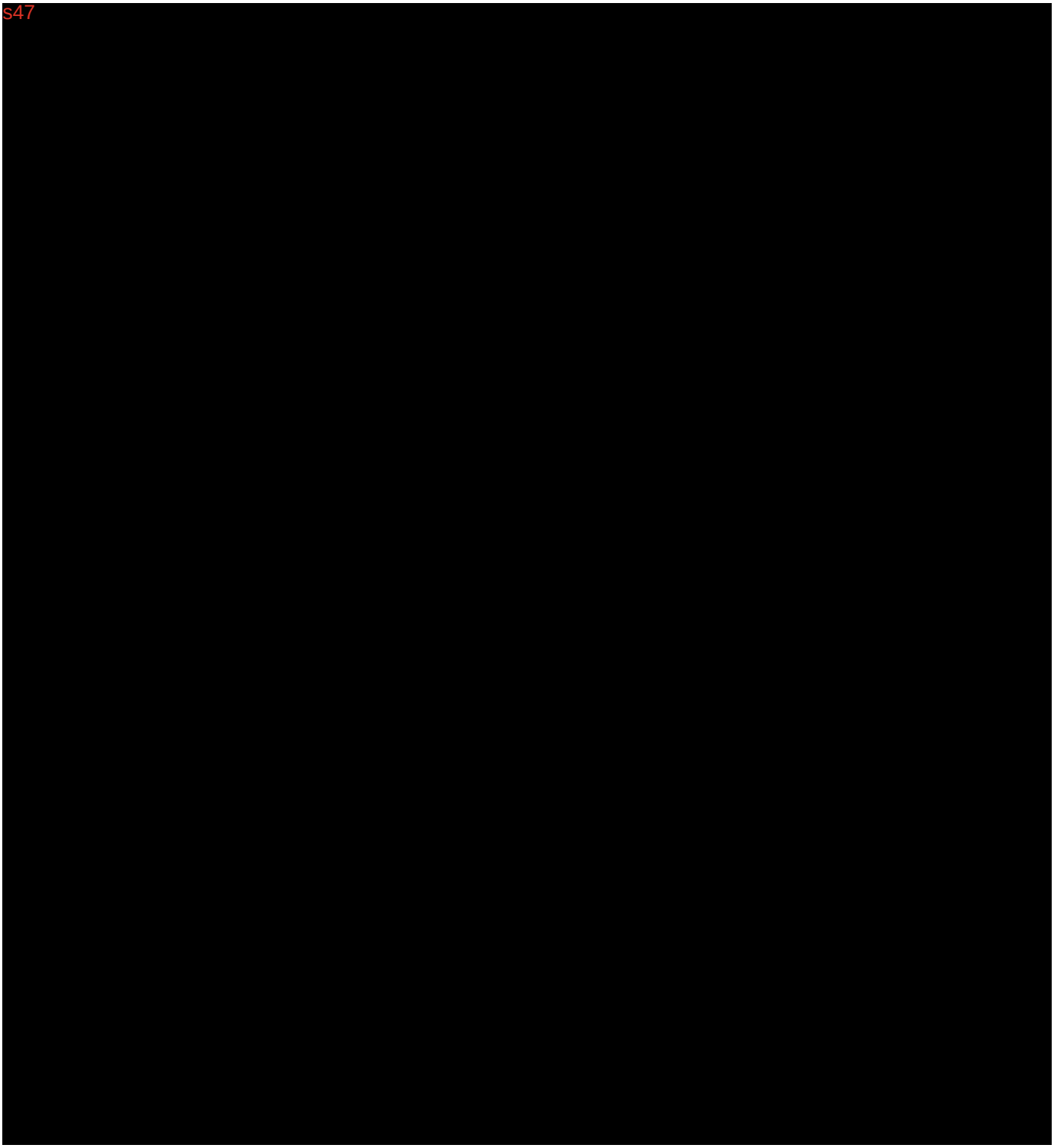

The nonclinical studies were conducted with the drug substance produced at a small-scale (10 L); which according to the Sponsor s47 [redacted]. However, it appears that the manufacturing process as well as manufacturing sites have changed since completion of the nonclinical studies. The DS/DP used in the nonclinical studies might not be comparable with the product to be marketed in Australia. The Sponsor has been requested to comment on the following questions:

1. Please provide information on differences between the batches (including antigen, final formulation and adjuvant) used in nonclinical studies and commercial batches to be marketed in Australia.
2. Are there nonclinical studies assessing the comparability of the nonclinical and commercial batches? If not, please provide justifications for not conducting nonclinical comparability studies between the manufacturing sites, including a discussion on the impact of any differences on efficacy and safety of the vaccine.

Sponsor's response to the above questions (received on 16 December 2021):

The response provided by the Sponsor (in a non-eCTD format) is not considered to adequately address the questions above.

The Sponsor indicated that there was no difference in antigen, final formulation, or adjuvant in the drug product batches used in non-clinical studies conducted in Non-Human Primates (2020-08-702-094, 2020-11-702-099, and 702-111) compared to the batches used in clinical studies or the batches proposed for commercial use in GMP (Good Manufacturing Practice) facilities. The Sponsor noted that the drug substance produced at s47 [redacted] were shown to be comparable based on Module 3 data, and also additional mouse immunogenicity studies comparing nonclinical and clinical batches of drug substance and drug product. However, 6 immunogenicity studies mentioned in the response could not be located in Module 4 of the dossier. Therefore, additional 3 questions were communicated to the Sponsor (see below).

s47 [redacted]

The Sponsor's response to Questions 1–3 was received on 24th December 2021.

1. Several studies mentioned in the Sponsor's S31 response cannot be located in Module 4. The Sponsor is requested to provide these studies: mouse immunogenicity studies (2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, 2021-22-702-132 and 702-157) and nonclinical study in non-human primate (702-111).

Sponsor's response to Question 1:

The Sponsor submitted the reports for studies 2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, and 2021-22-702-132 noted in the above response and indicated that "*Studies 702-157 and 702-111 are in the reporting phase and reports will be available in Q2 2022*."

Nonclinical assessment of the Sponsor's response to Question 1:

Studies 2020-10-702-100/107, 2020-12-702-113, 2021-17-702-119, 2020-20-702-126, and 2021-22-702-132 have been evaluated in the present report (see Section 2.2.1).

2. Can the Sponsor provide a comparison between the manufacturing processes used to produce the batches tested in the nonclinical studies and the manufacturing processes used to produce the commercial batch(es) that will be released in Australia; in terms of DS (antigen, Matrix-M1) and DP (vaccine)?
    a. In what are they similar?
    b. In what do they differ?
    c. How can these differences affect safety and efficacy?

Sponsor's response to Question 2:

The Sponsor indicated that the manufacturing process for producing the purified antigen "*in the Novavax Discovery laboratories for use in nonclinical studies was substantially similar to the process used at SIIPL* [Serum Institute of India Pvt. Ltd.] *for the commercial lots*". Table 1.7 lists the similarities and differences in DS and DP manufacturing processes for the batches used in the nonclinical studies and the commercial batch(es) for release in Australia.

Antigen:
The Sponsor indicated that the differences in the antigen manufacturing process were represented in one clinical batch (FDBU 2000 L). The Sponsor specified that efficacy was demonstrated in the clinical studies conducted with this batch and no safety concerns were identified.

Matrix-M1:
The Sponsor stated that "*the Matrix-M1 batches used in the nonclinical studies… were mixed from Matrix-A and Matrix-C adjuvant components manufactured at the Novavax AB site in Uppsala, Sweden (NVX-AB)* s47 [redacted]
The Sponsor indicated that "*A comprehensive analytical comparability package demonstrated comparability across Matrix-A and Matrix-C batches manufactured at the* s47 [redacted]

Vaccine:
The Sponsor notified that "*BV2373 antigen lot Discovery 16Apr20 (produced by Novavax, Inc. at laboratory scale)*" and "*The adjuvant lots (M1-108 and M1-111…)…*s47 [redacted] *by Novavax AB"* used in two NHP nonclinical studies (Study 702-094 in cynomolgus macaques and Study 702-099 in rhesus macaques) "*were also used in clinical studies*". "*The DP processes used for both the non-clinical lots and the commercial batches involve the use of DS and Matrix – formulated with a buffer of 300mM Sodium Chloride, 25mM Sodium Phosphate, and 0.01% PS80, at a pH of 7.2. In addition to the scale difference noted above, other differences in the DP process include:*

- *Use of pre-formulated Matrix-M1 for non-clinical lots and the use of separate Matrix A and Matrix C fractions for commercial lots.*
- *PS80: Croda Highly Purified and/or Super Refined grade was used for non-clinical lots and NOF will be used for commercial lots.*

None of these changes are considered to be significant and will not affect safety or efficacy."

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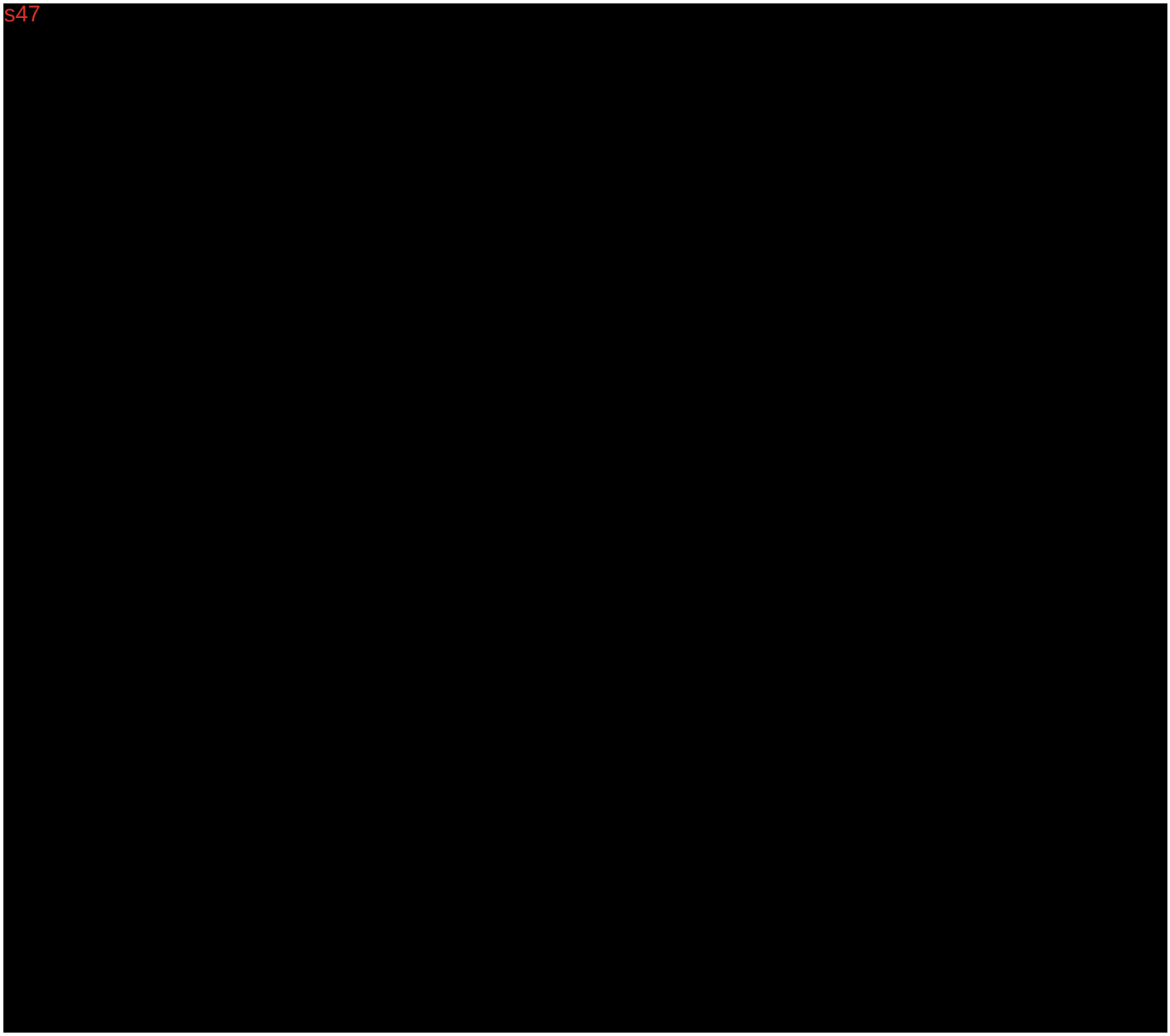

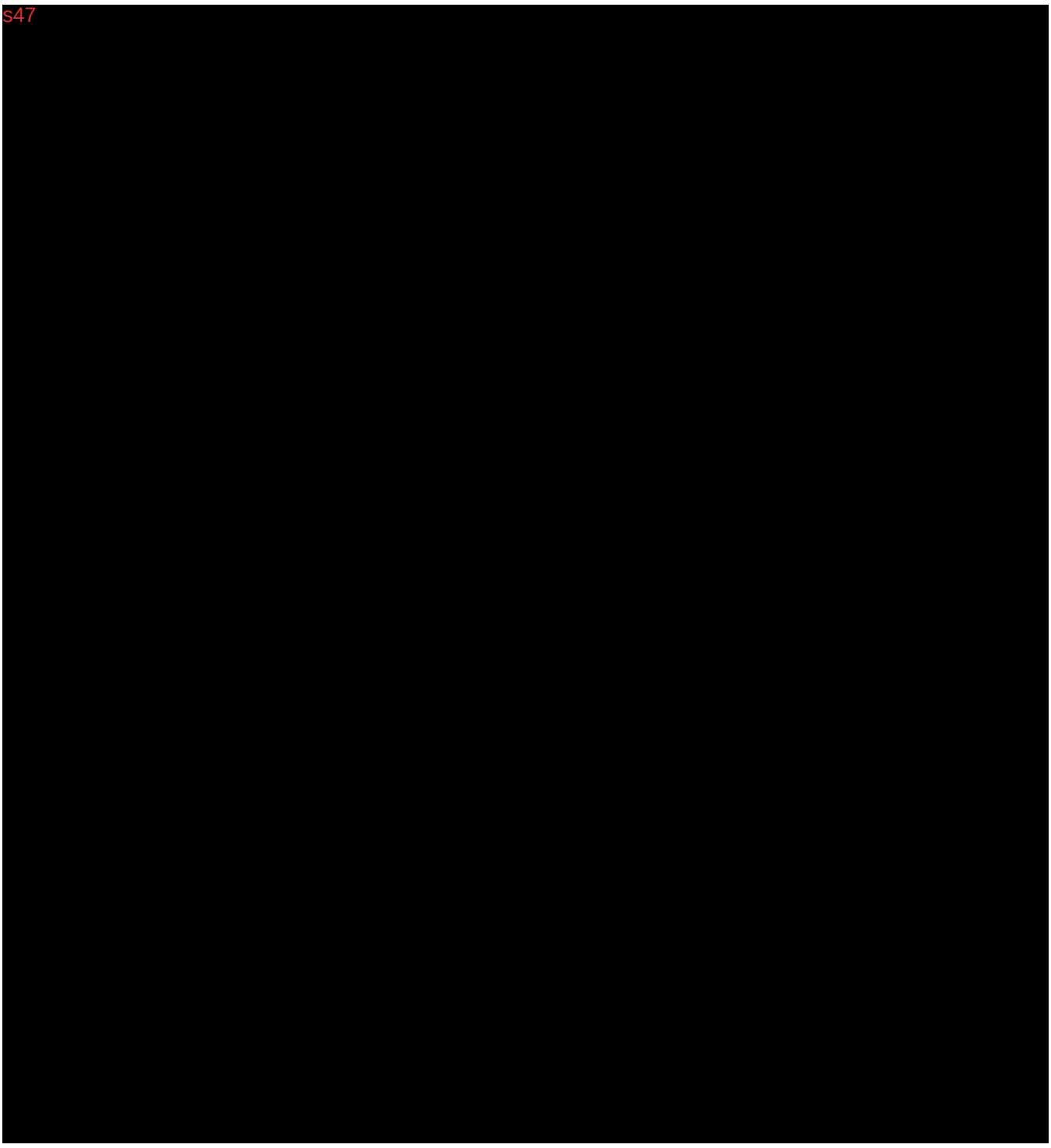
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Nonclinical assessment of the Sponsor's response to Question 2:

Based on the data provided by the Sponsor the manufacturing processes used to produce the antigen (rS protein), adjuvant (Matrix-M1) and vaccine appear to have substantially changed throughout the development of the DS and DP. The quality (Module 3) data for the DS and DP are currently under evaluation. s47 [redacted]

s47 [redacted]

The Nonclinical Evaluator notes that Matrix-M1 batch M1-108 has been used in several clinical studies. However, references to Matrix-M1 batch M1-111 could not be located in Module 2.5 (Table 2.5-2).

3. Have the commercial batch(es) that will be released in Australia been tested in nonclinical studies?
    a. If so, indicate in which studies and, if not already submitted to TGA, please provide the studies.
    b. If not, justify why nonclinical comparative studies have not been conducted.

Sponsor's response to Question 3:

The Sponsor stated that considering "*the robustness of the in vitro analytical assays and ethics concerns*", no nonclinical *in vivo* studies were conducted with the commercial batches. Instead, "*comparability testing of SIIPL lots has been performed using 19 analytical assays and these lots have been shown to be comparable to lots used in Phase 3 clinical studies*".

Nonclinical assessment of the Sponsor's response to Question 3:

The accuracy and reliability of the analytical assays mentioned in the Sponsor's response to Question 3 and therefore the comparability between SIIPL, clinical and nonclinical batches solely depend on the evaluation of the quality studies submitted (assuming the comparability studies/analytical assays have been submitted in Module 3).

1.8. OVERSEAS REGULATORY STATUS

A similar application has been made in the EU, UK, Canada and New Zealand (all between January and February 2021).

1.9. SCOPE OF NONCLINICAL DATA

Module 4 comprised nonclinical studies with the clinical formulation. As a rolling submission, interim nonclinical data have been provided. Finalised study reports are expected to be submitted later. Up to 28 April 2021, most nonclinical data have been provided and reviewed in this evaluation report, with only two long term immunogenicity studies and one tissue distribution study, which are ongoing, to be provided in future submissions.

[7] Albanese A., Tang P.S. and Chan W.C. (2012) The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu. Rev. Biomed. Eng. 14: 1–16.

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2. PRIMARY PHARMACOLOGY

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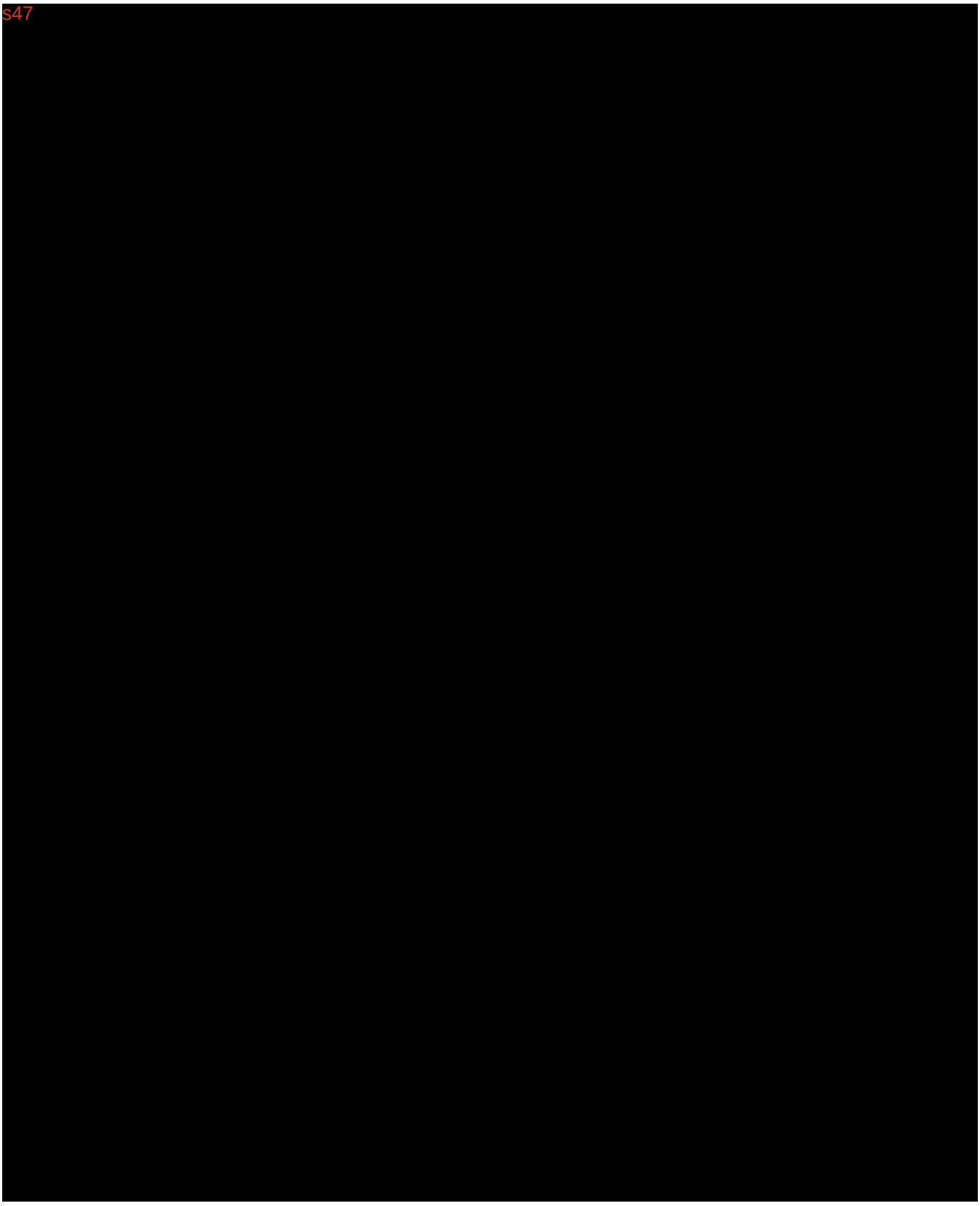

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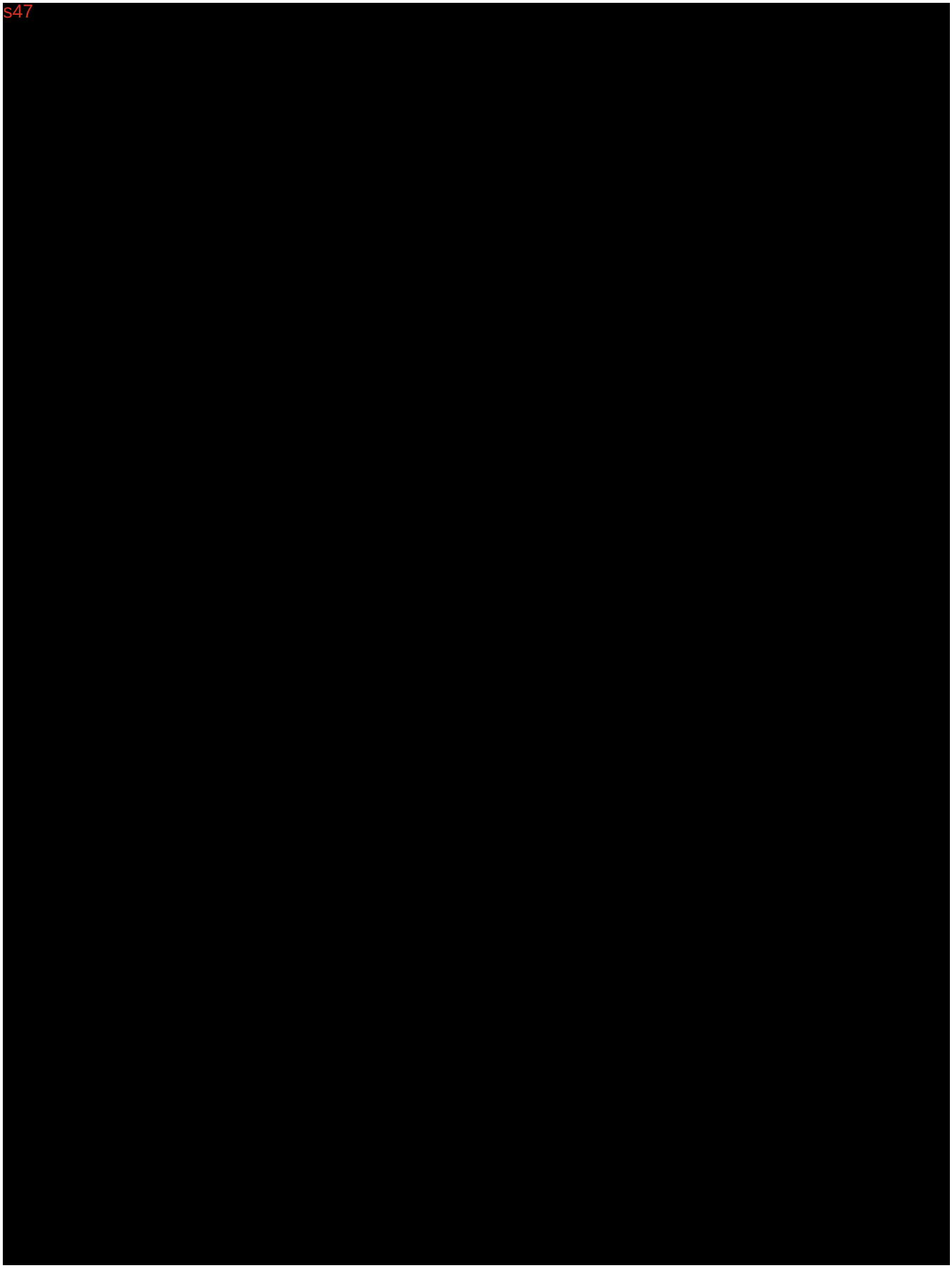

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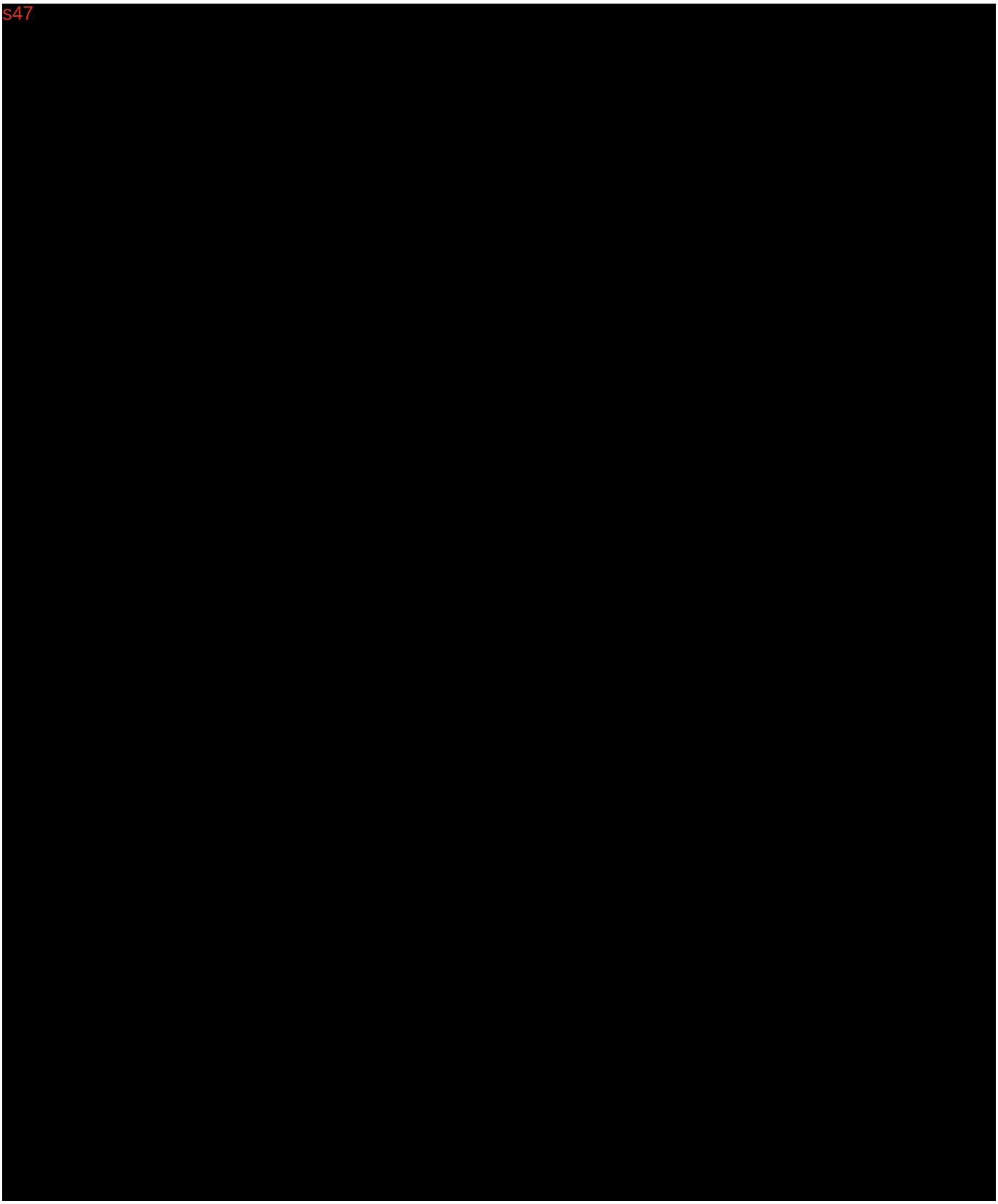

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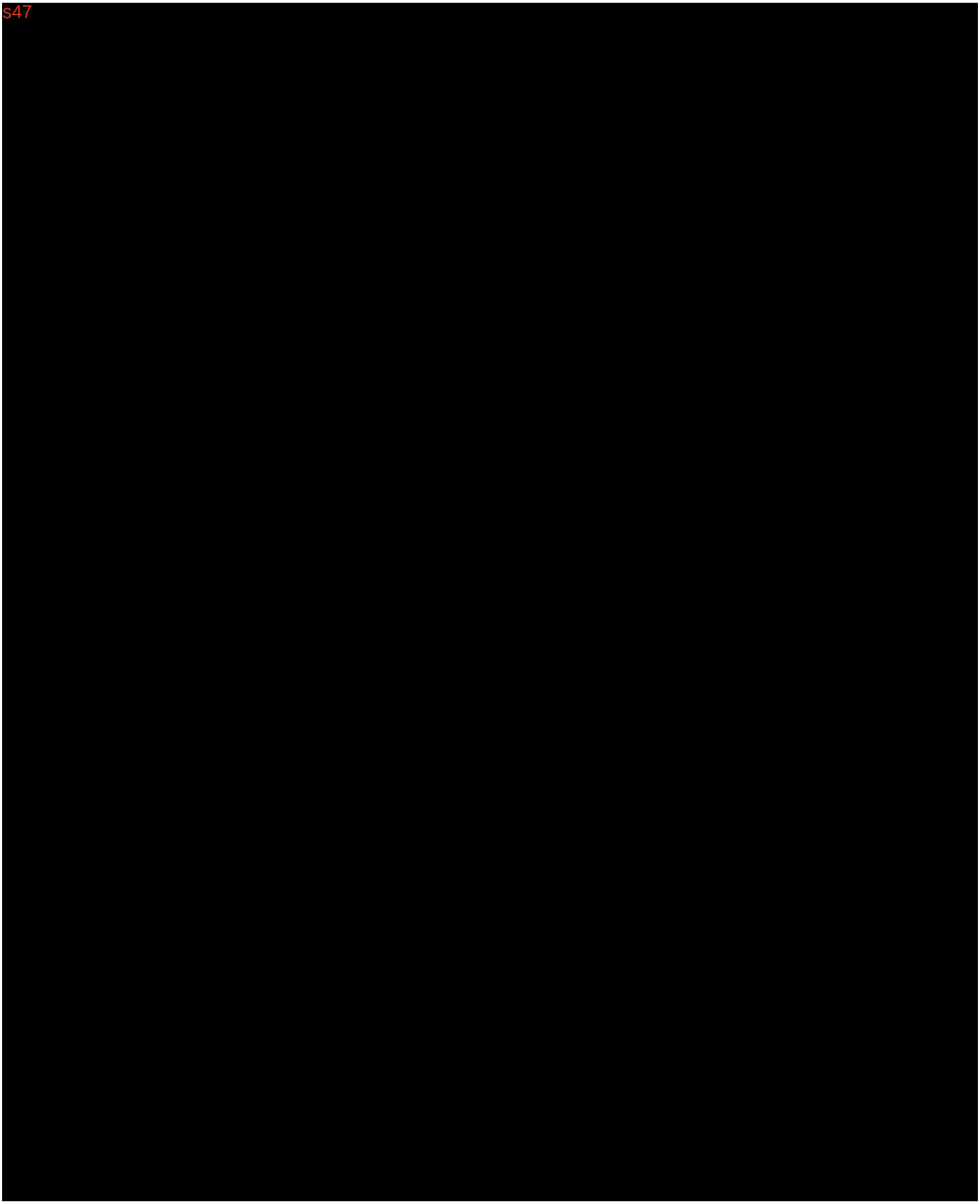


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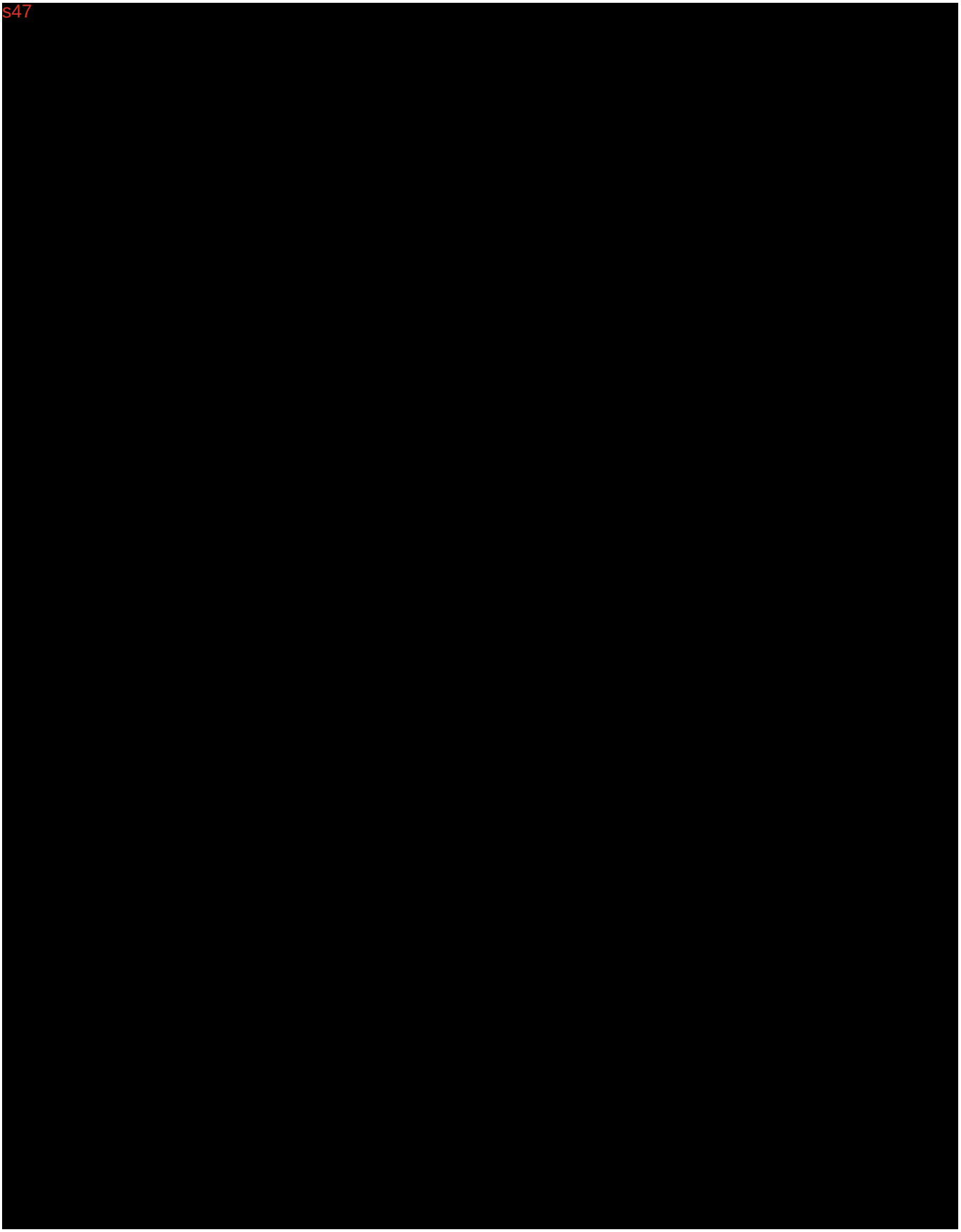

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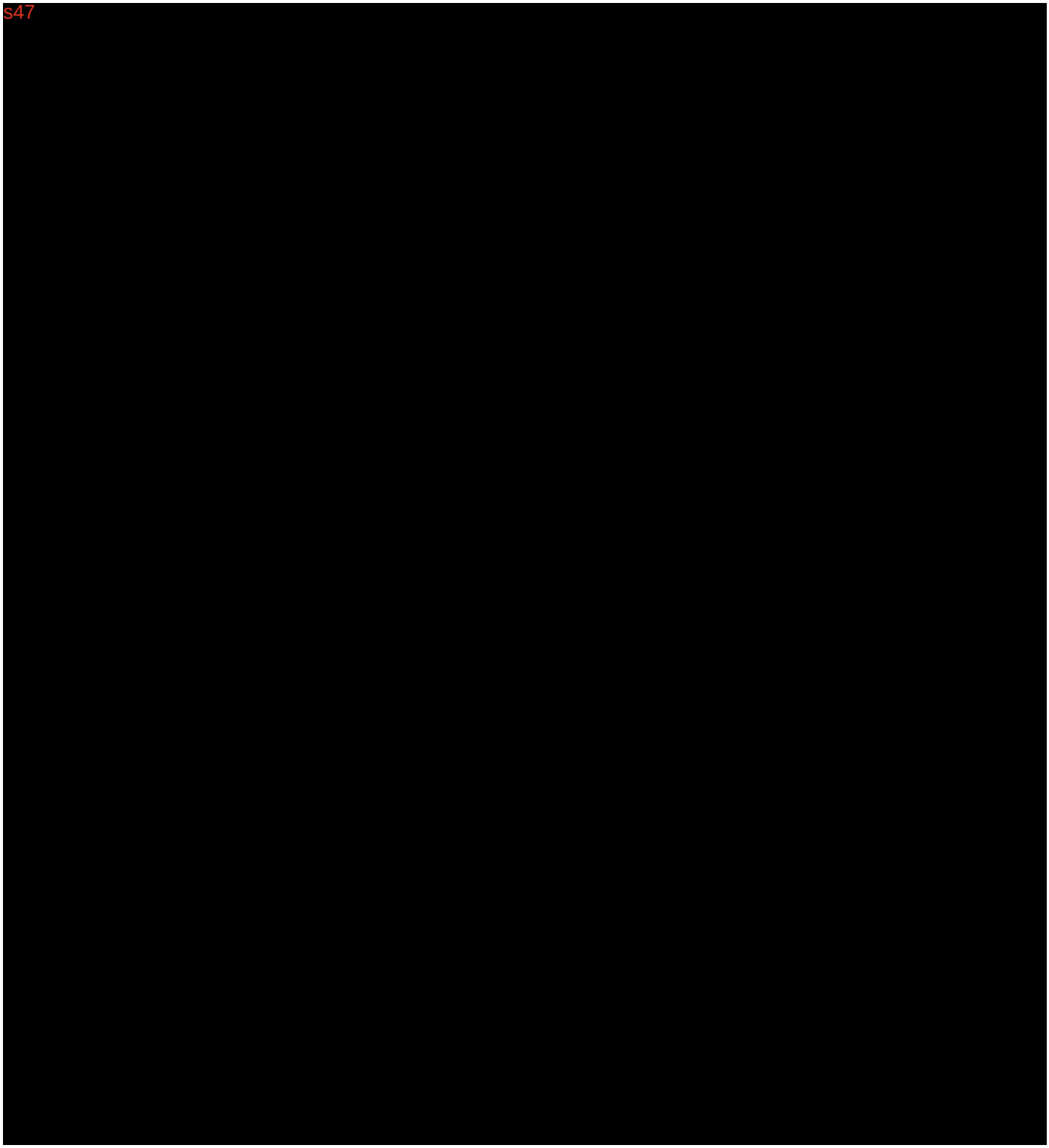

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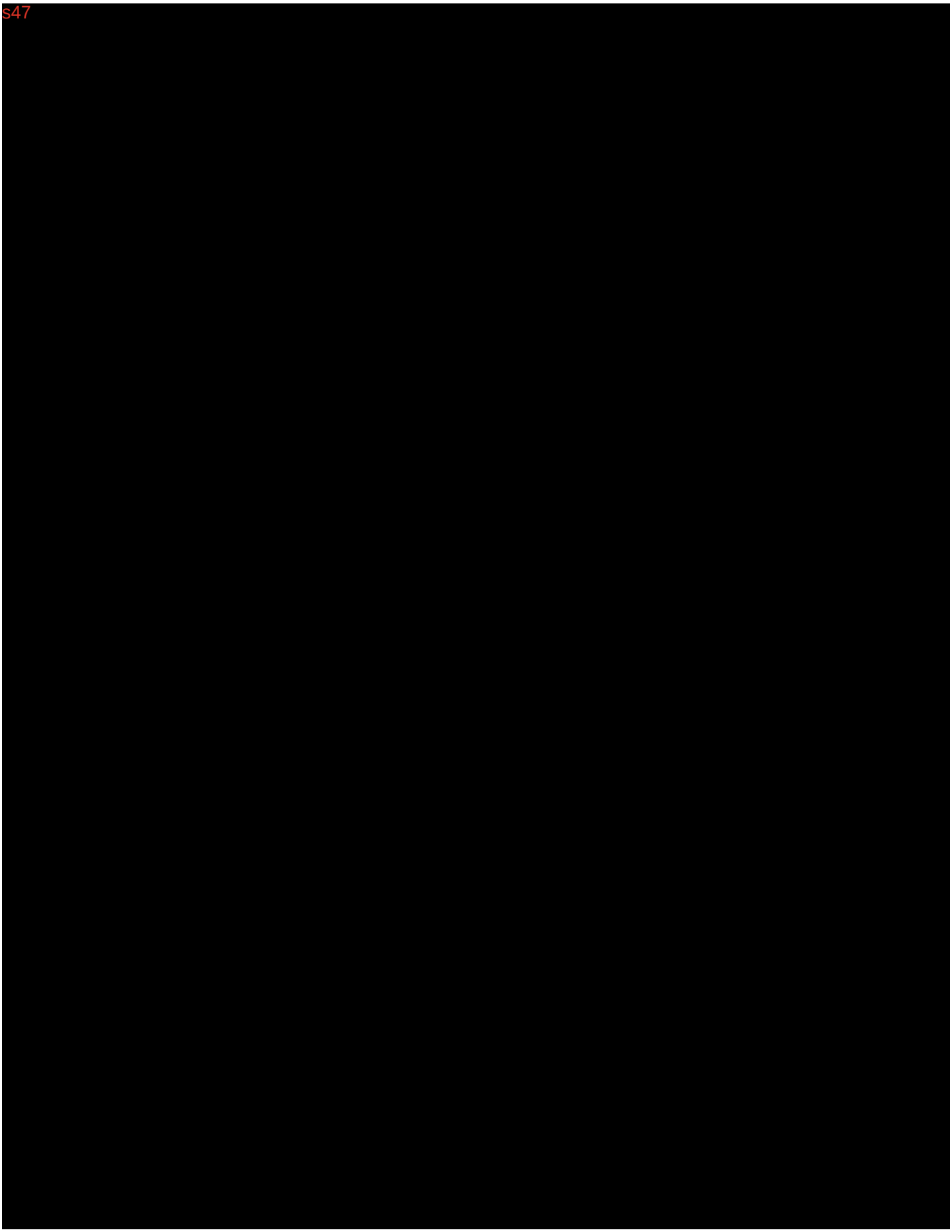

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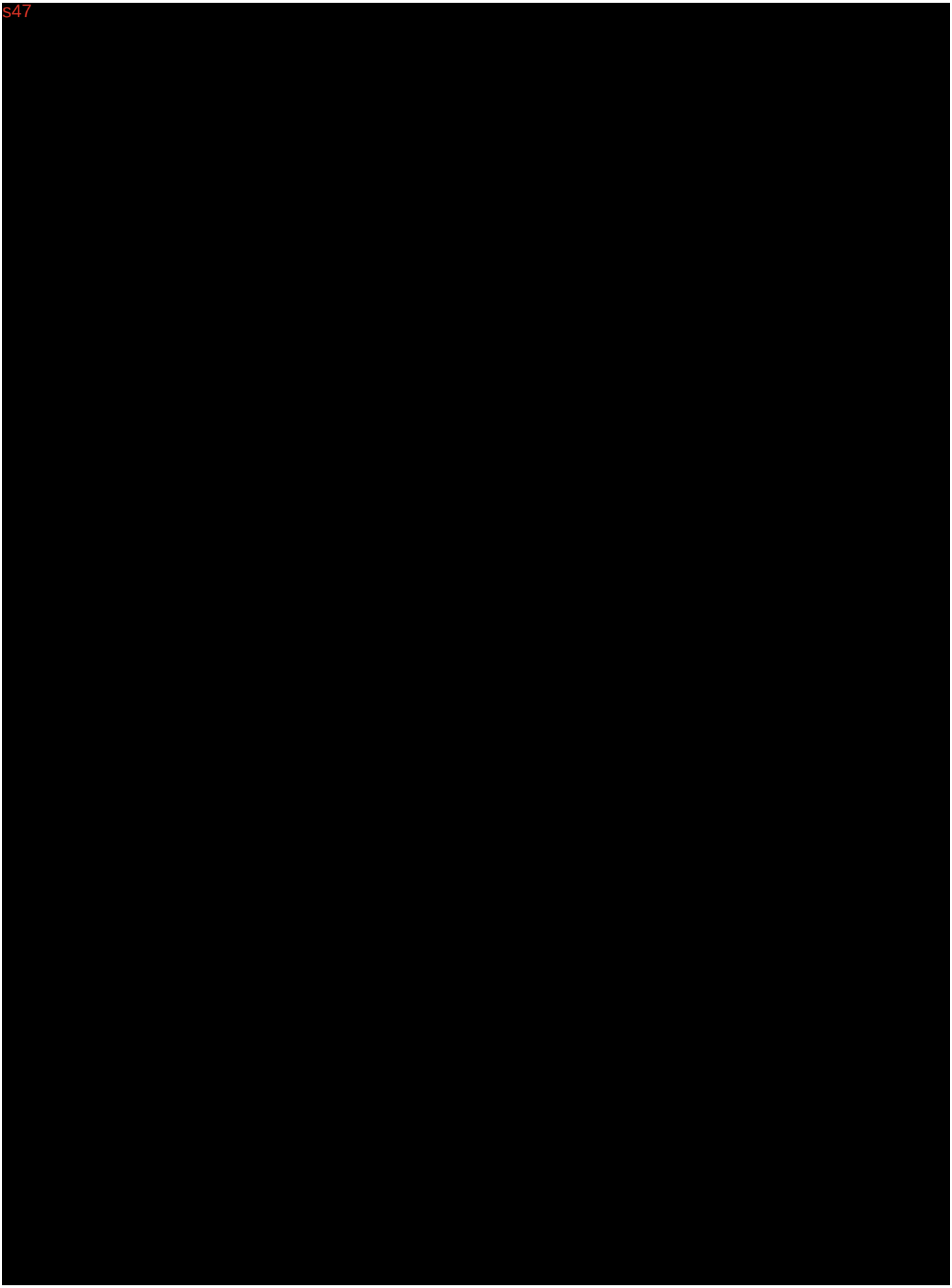

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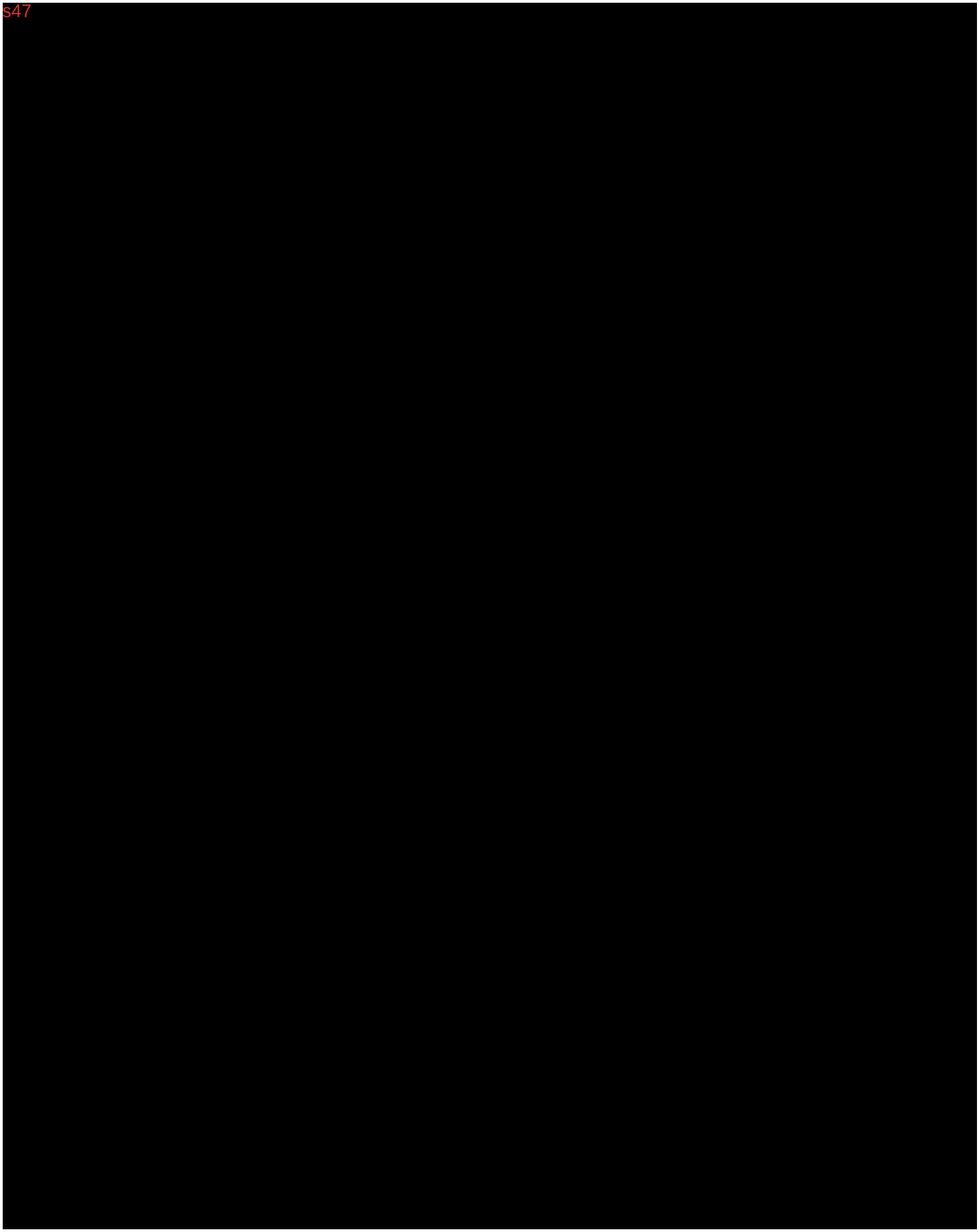

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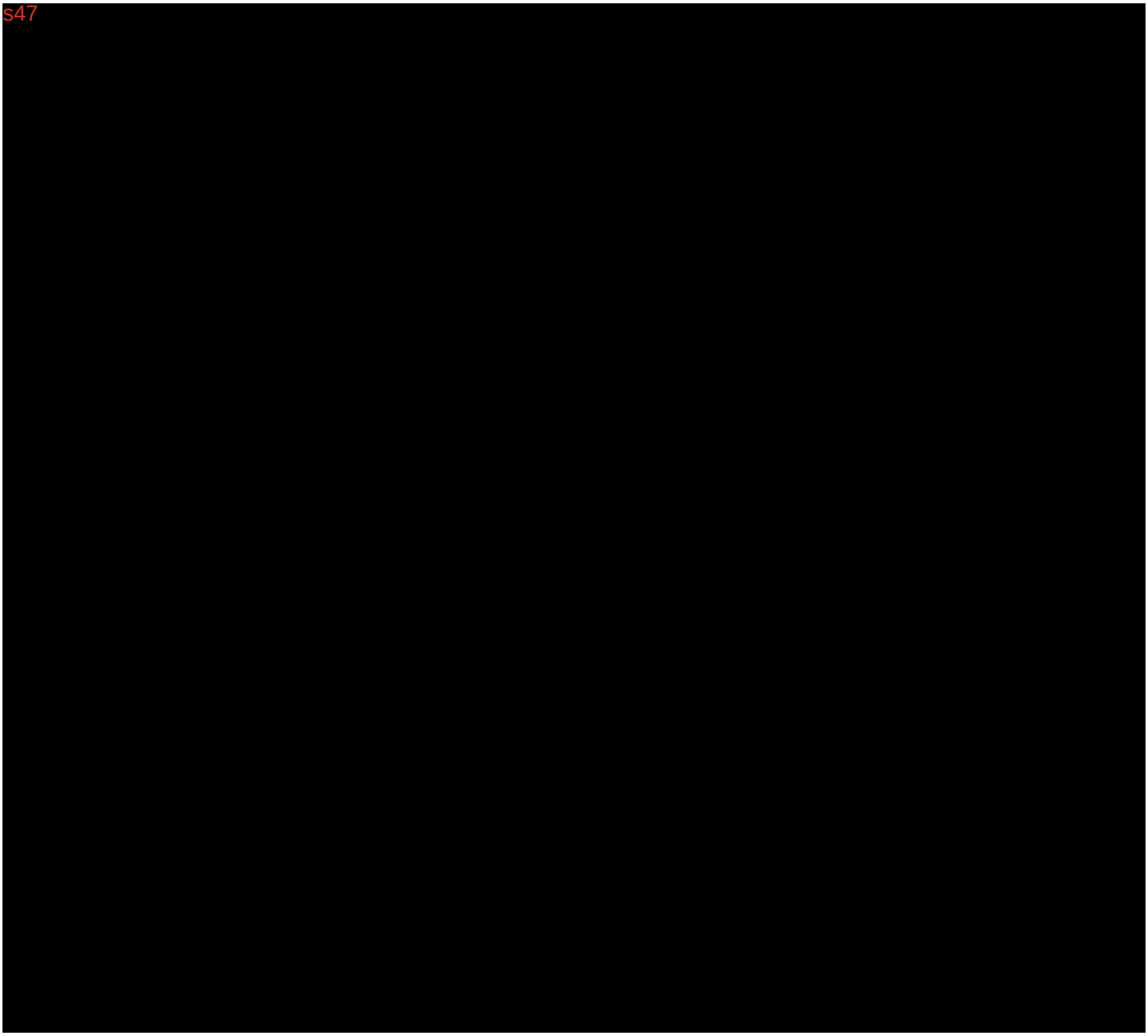

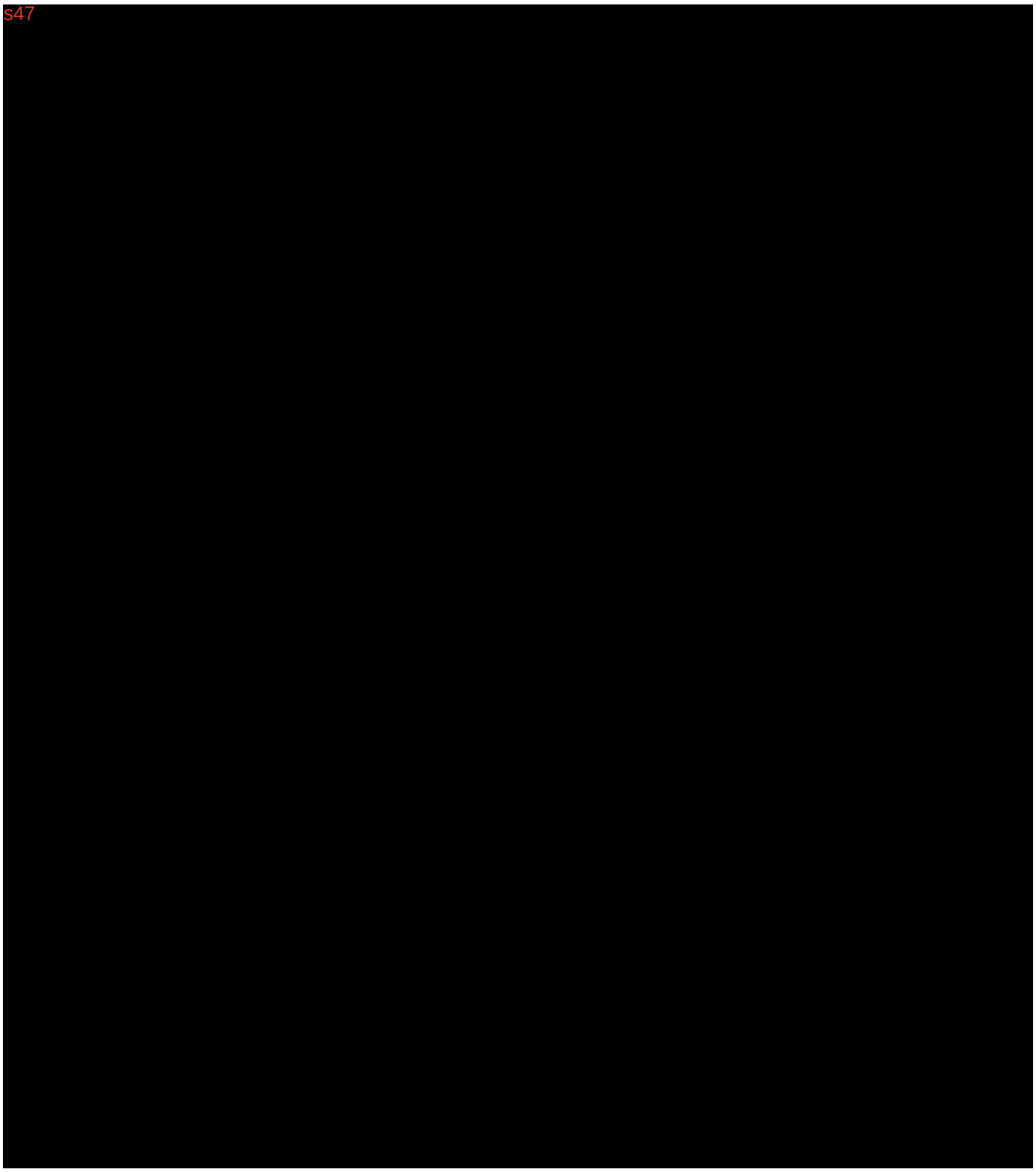
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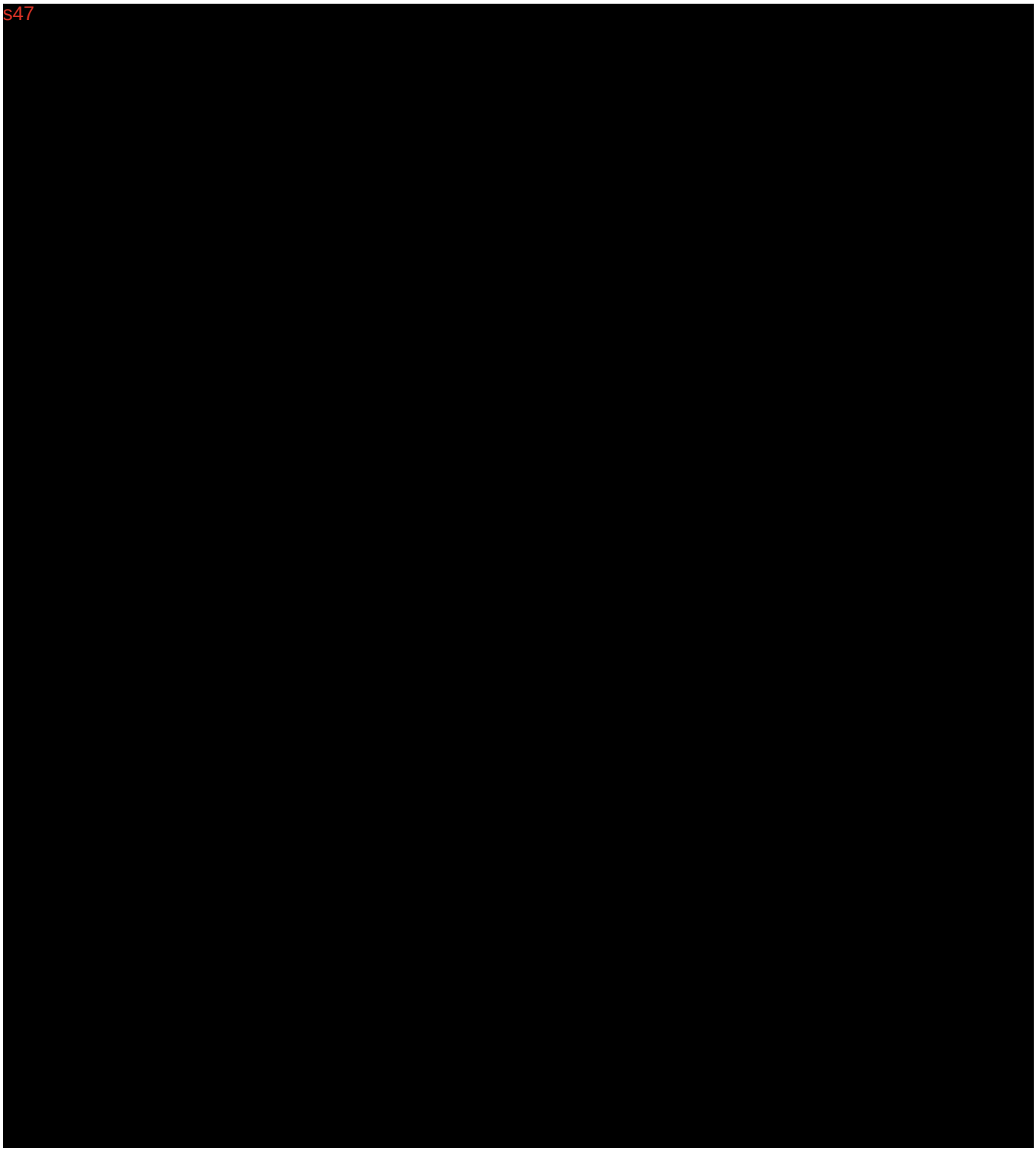

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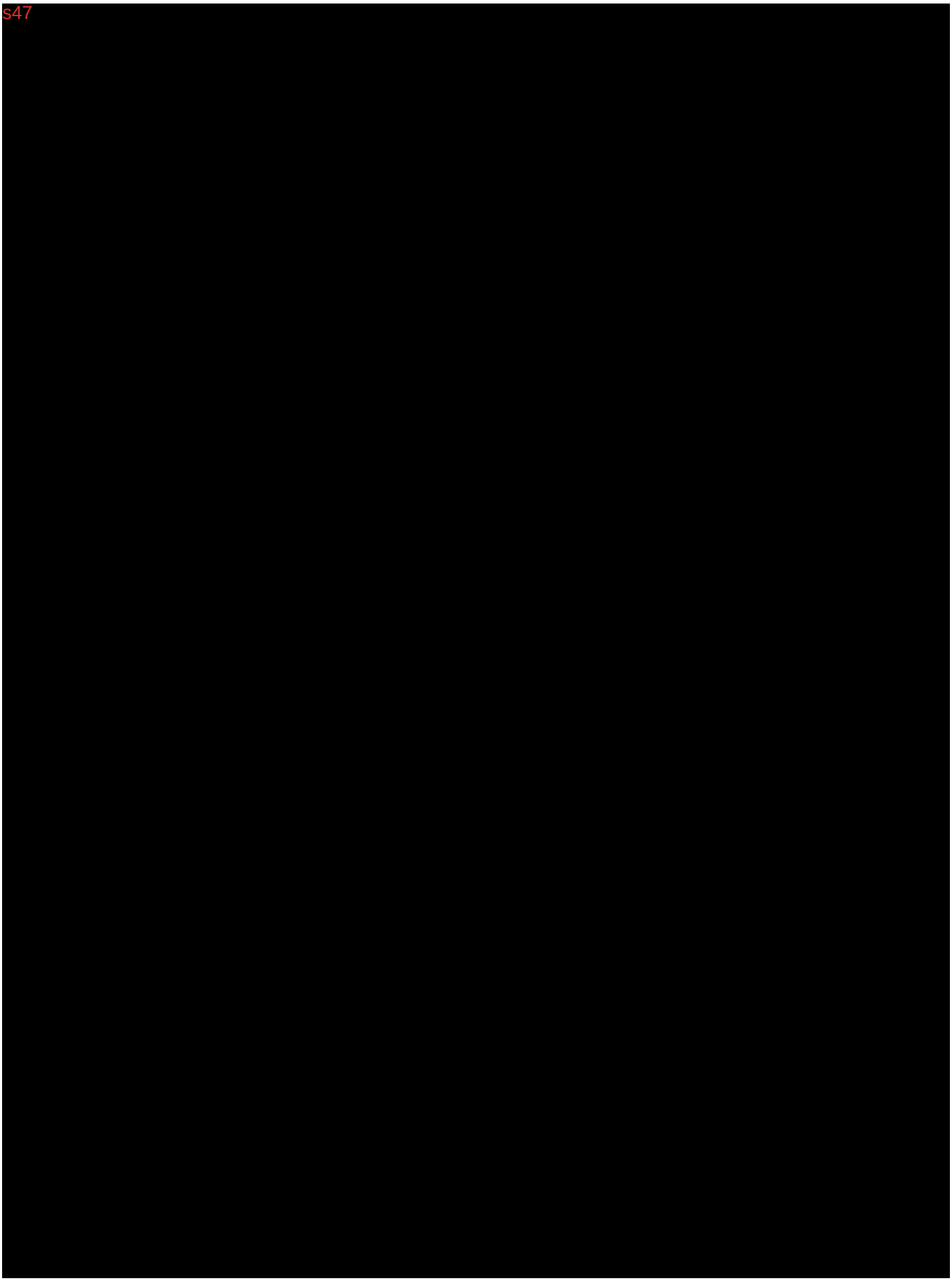

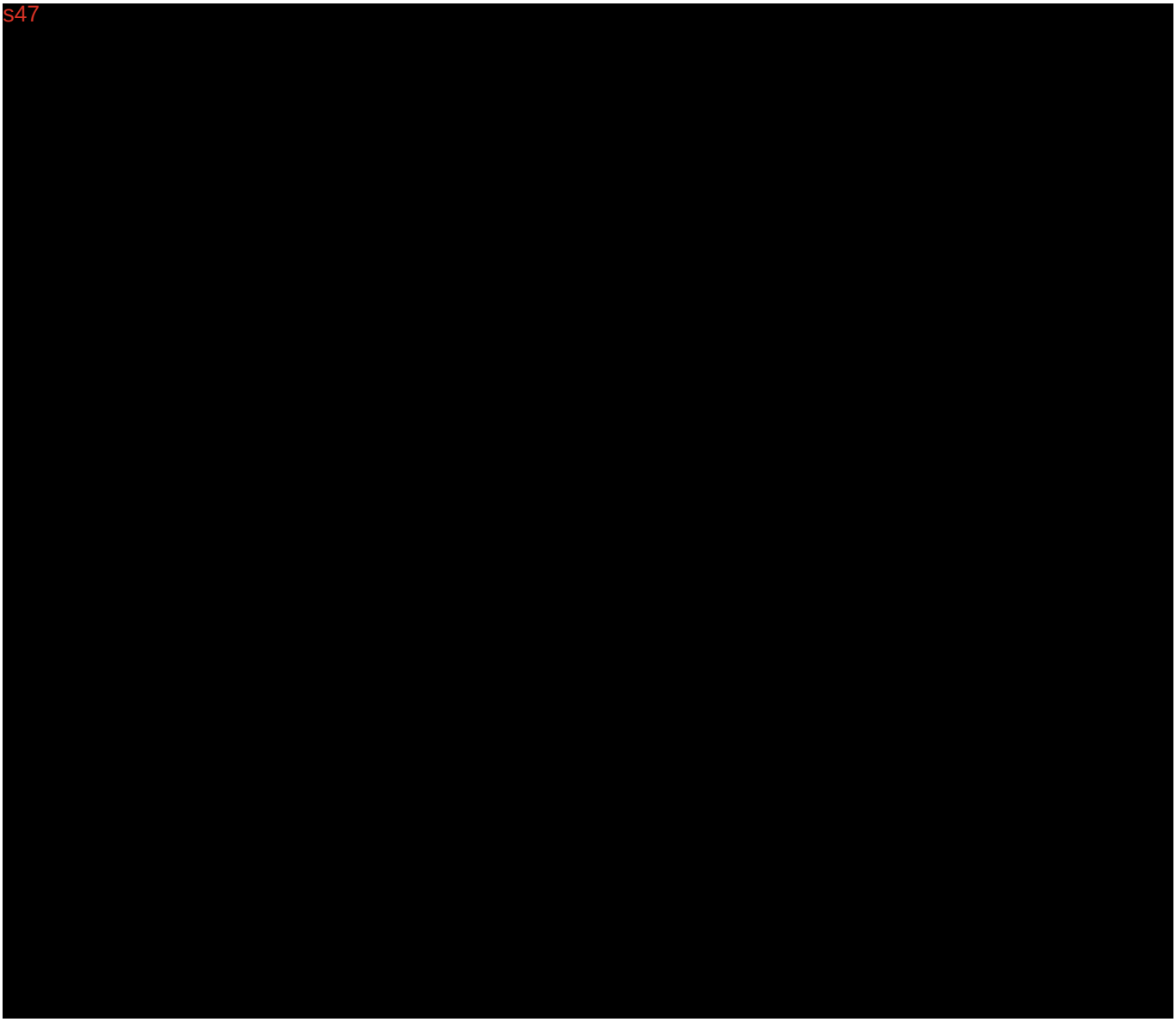
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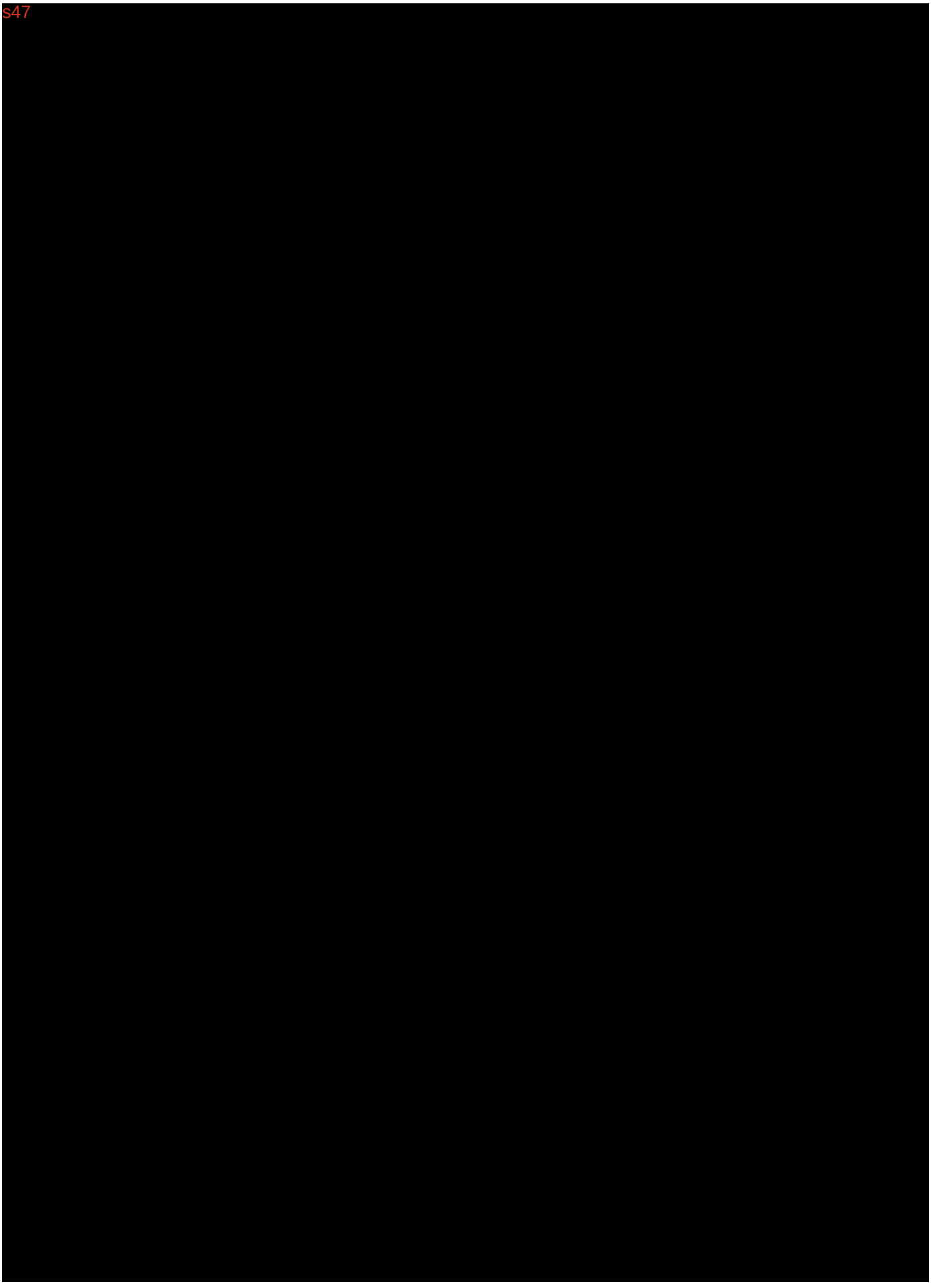

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[8] Probit Anaysis

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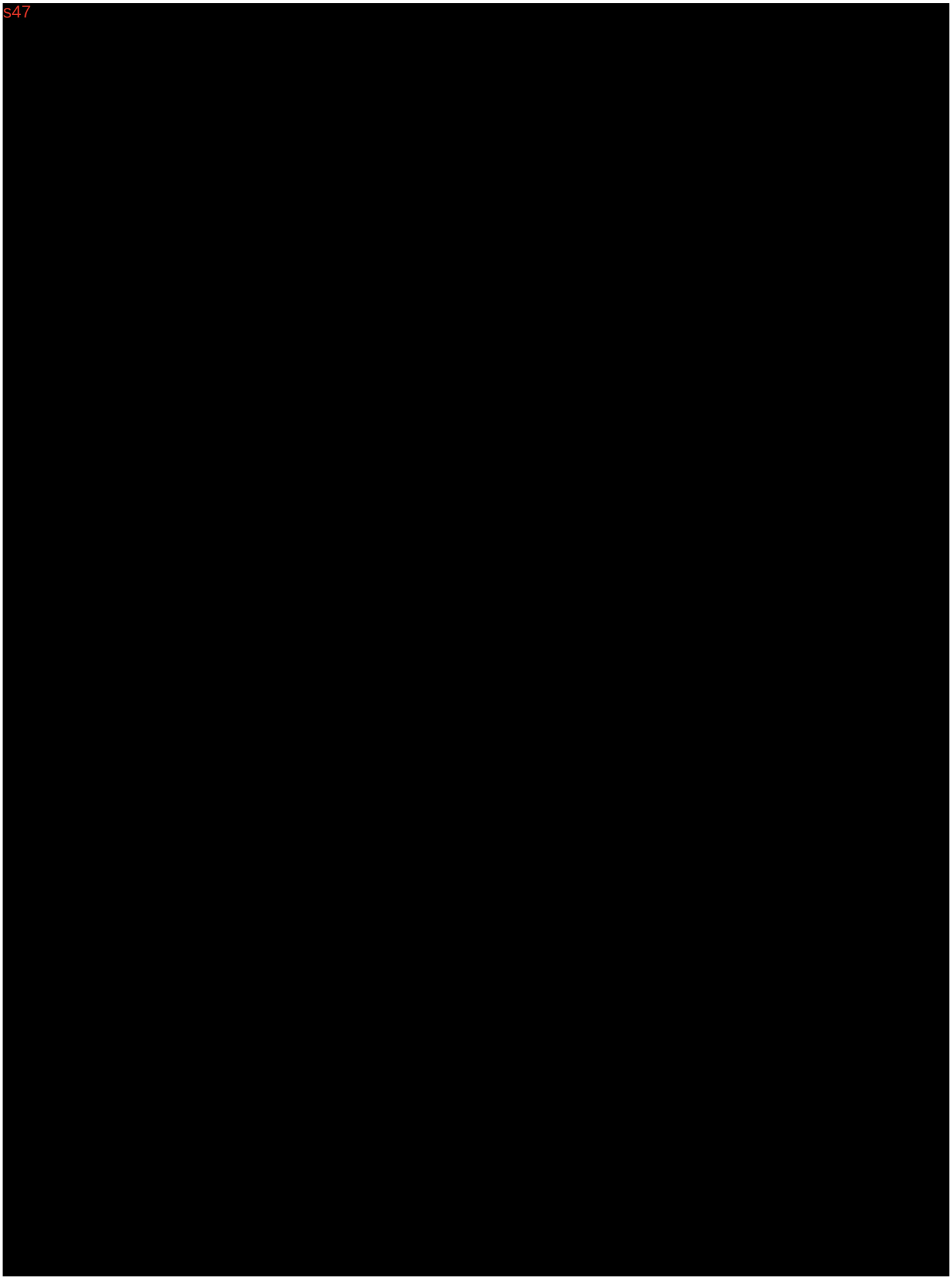

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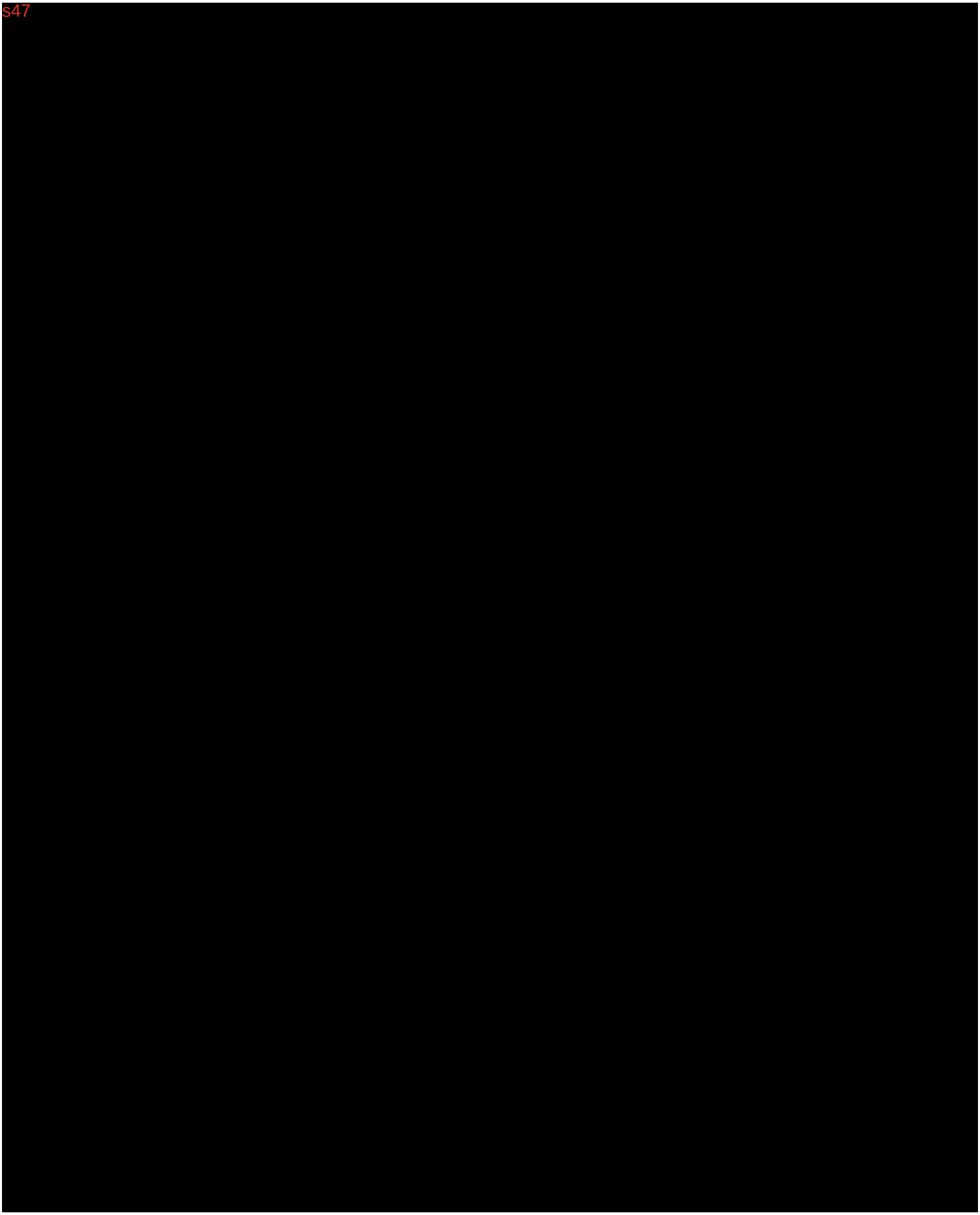

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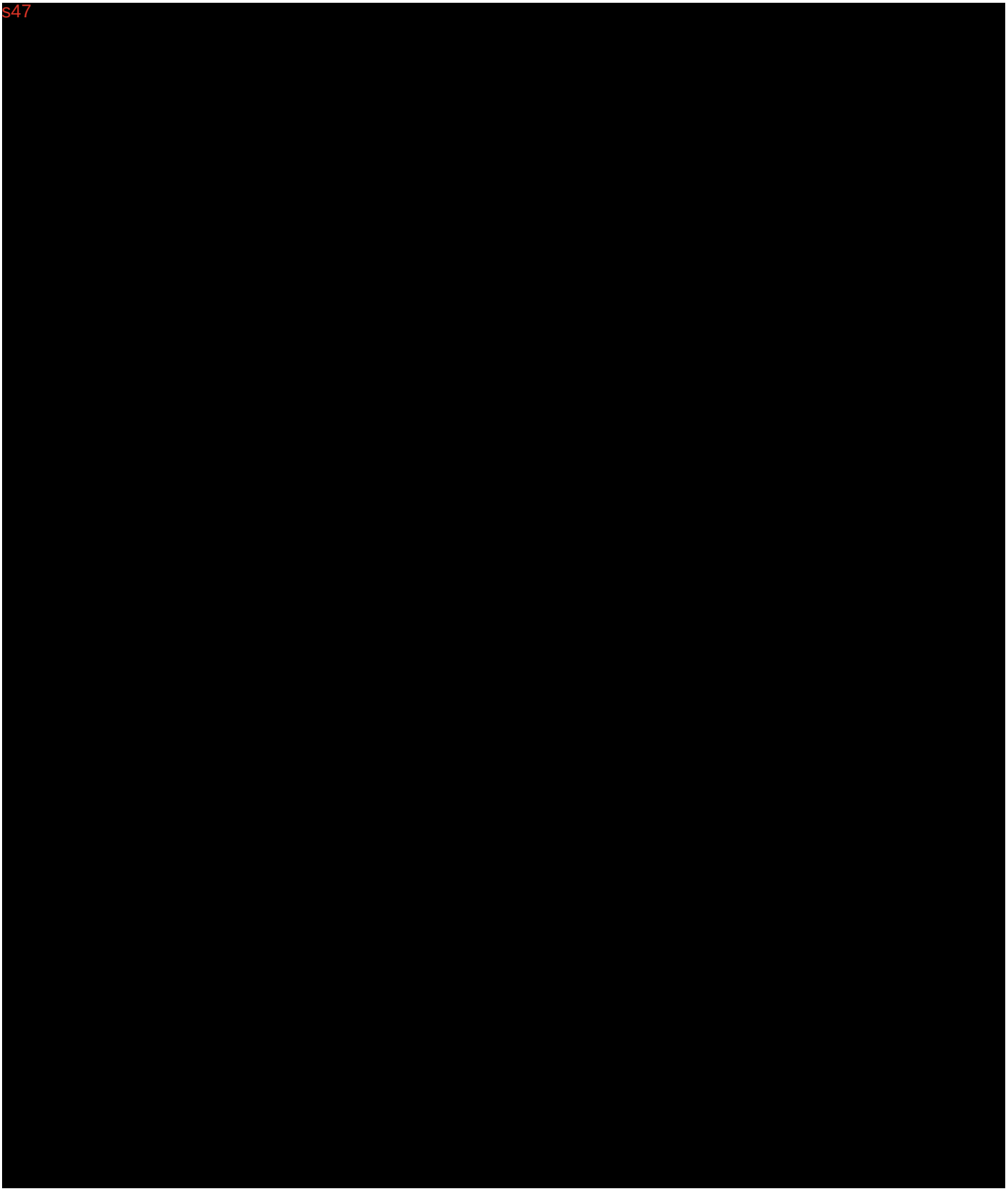

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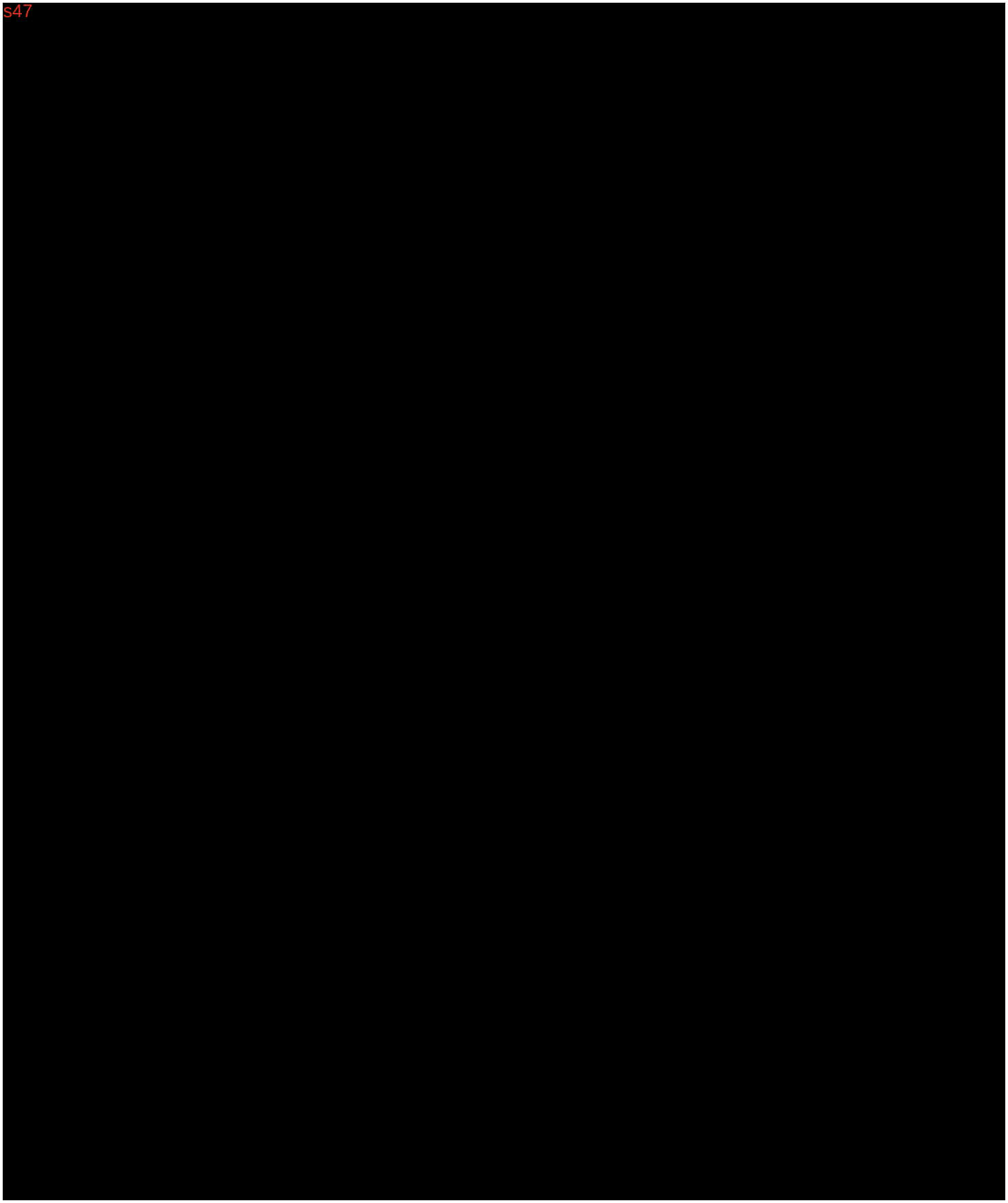

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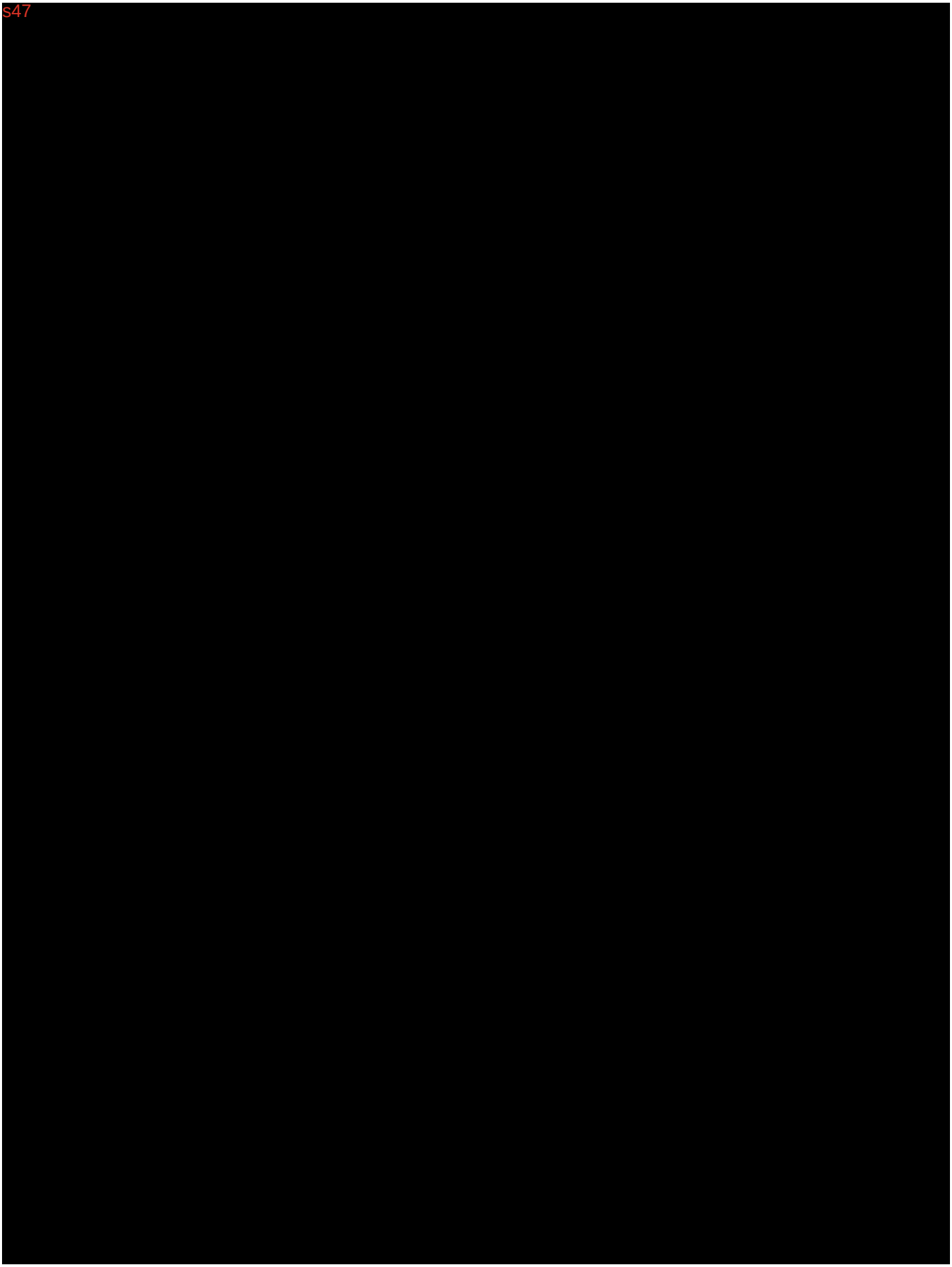

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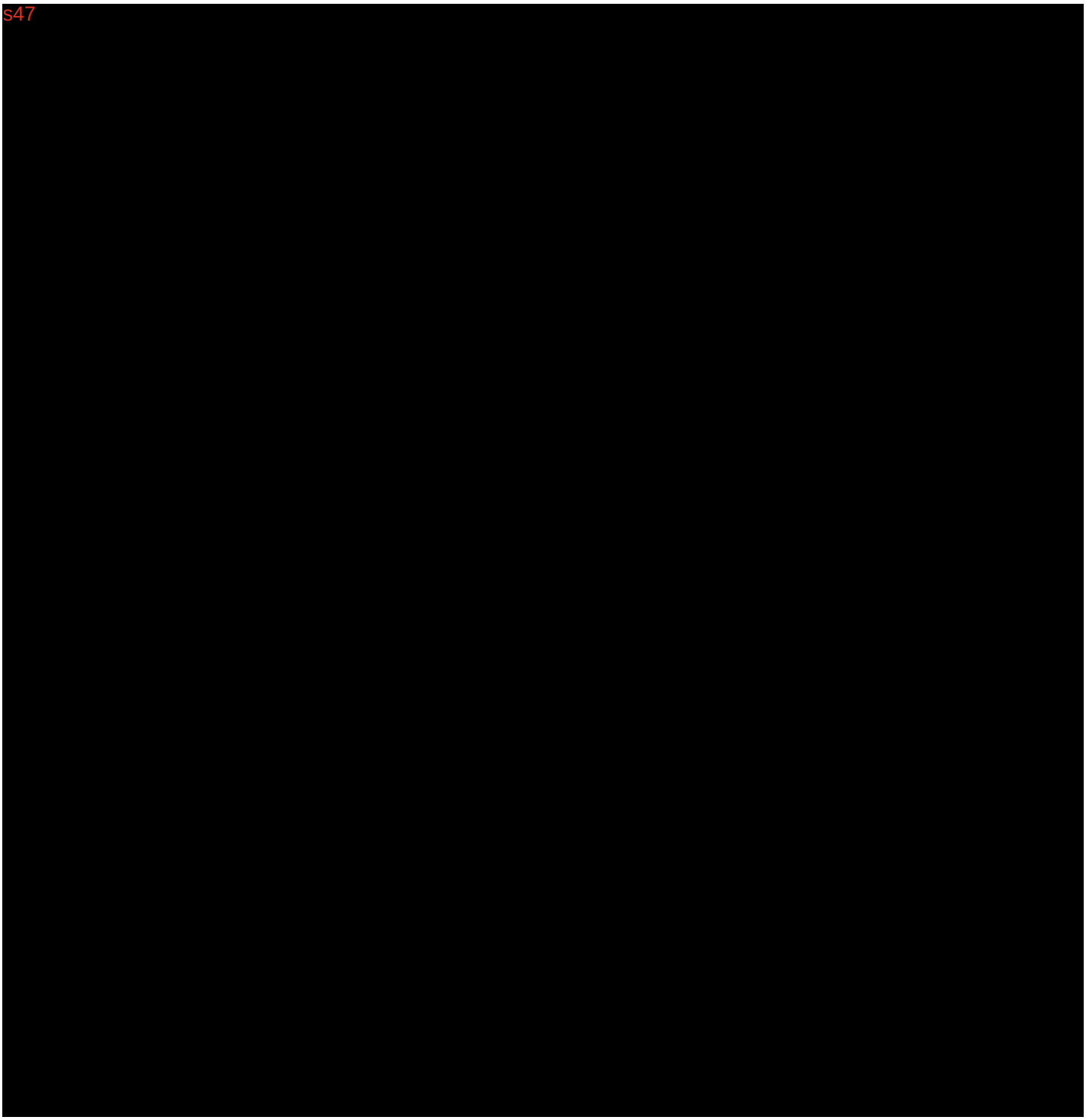

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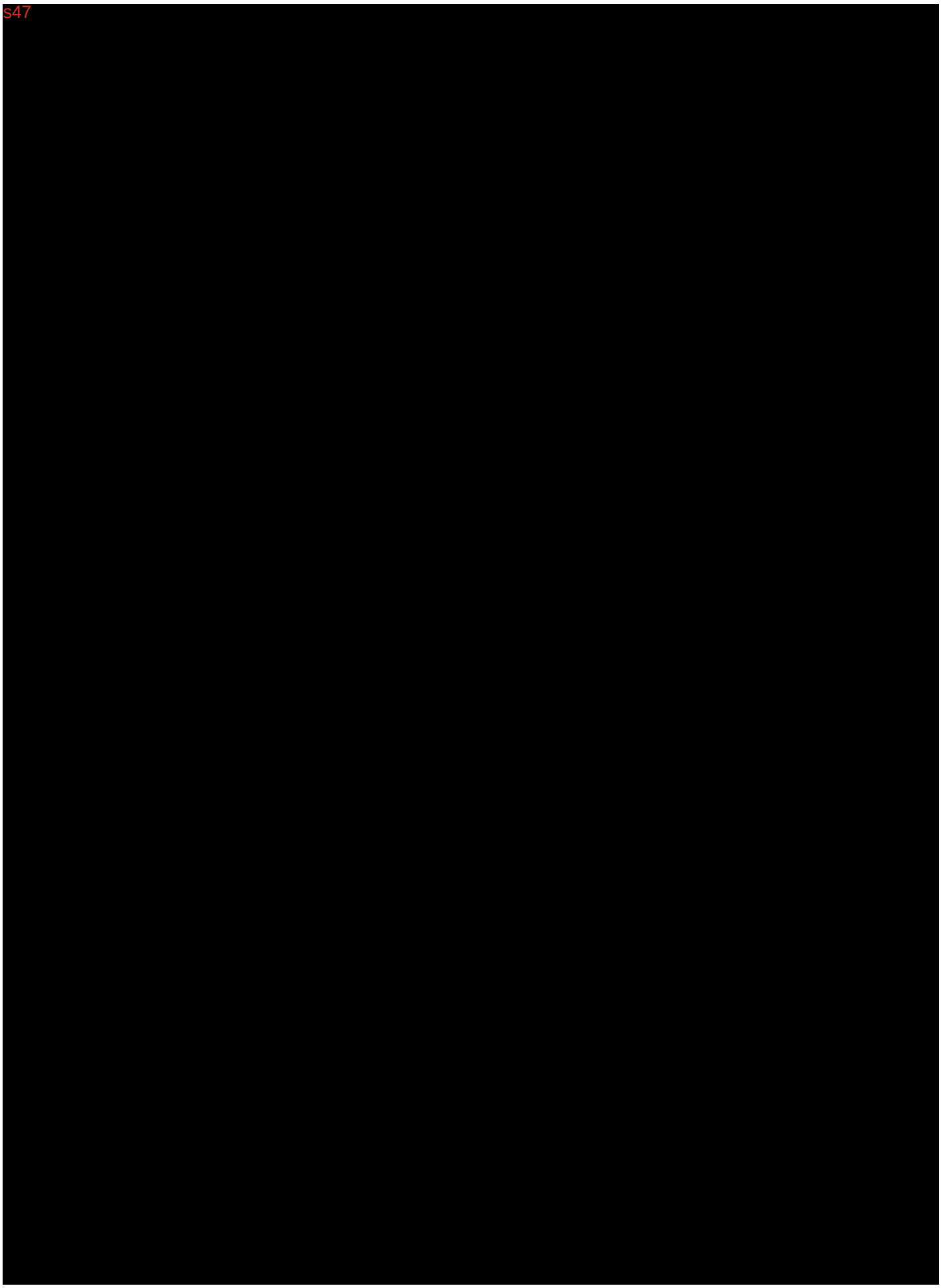

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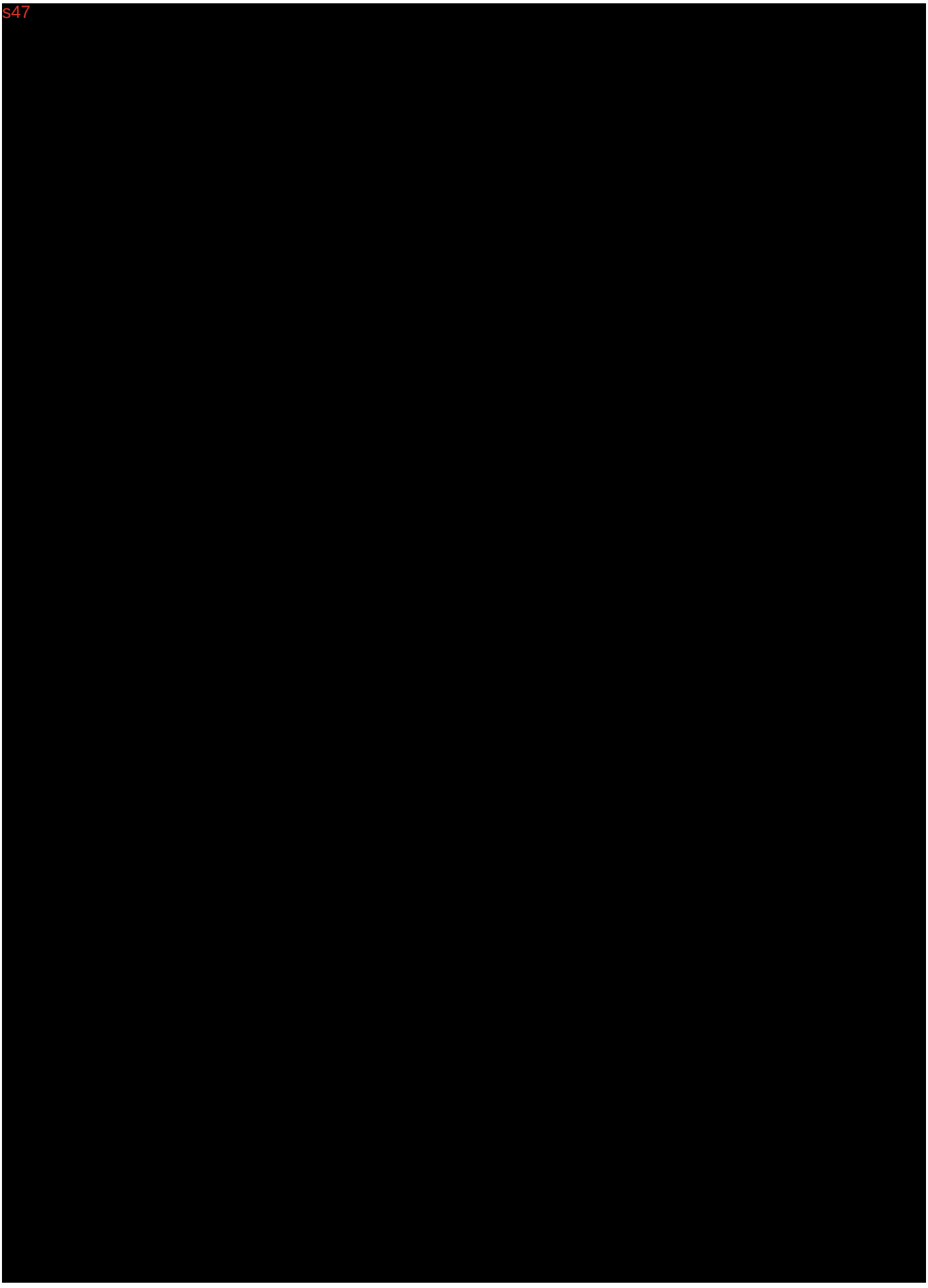

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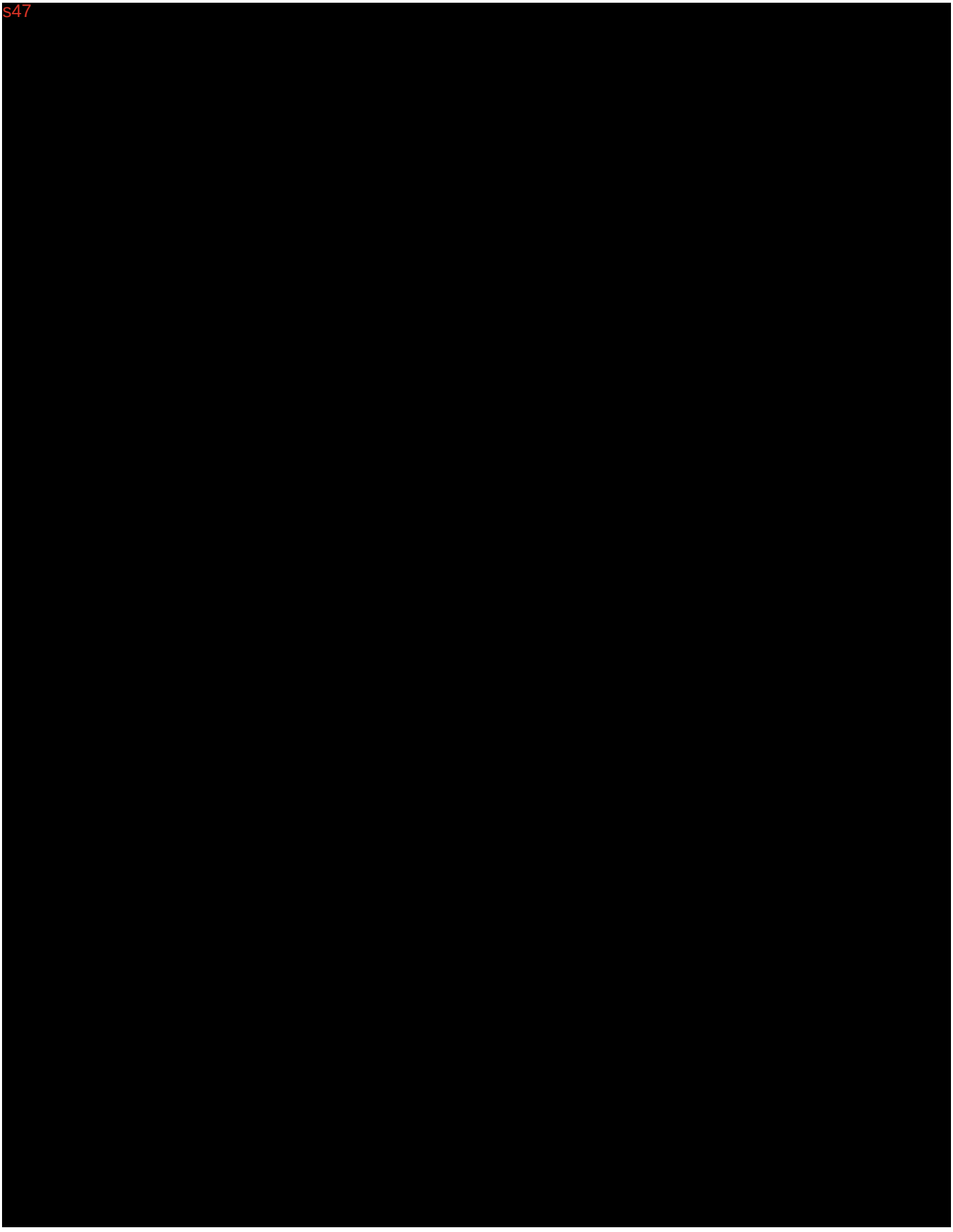

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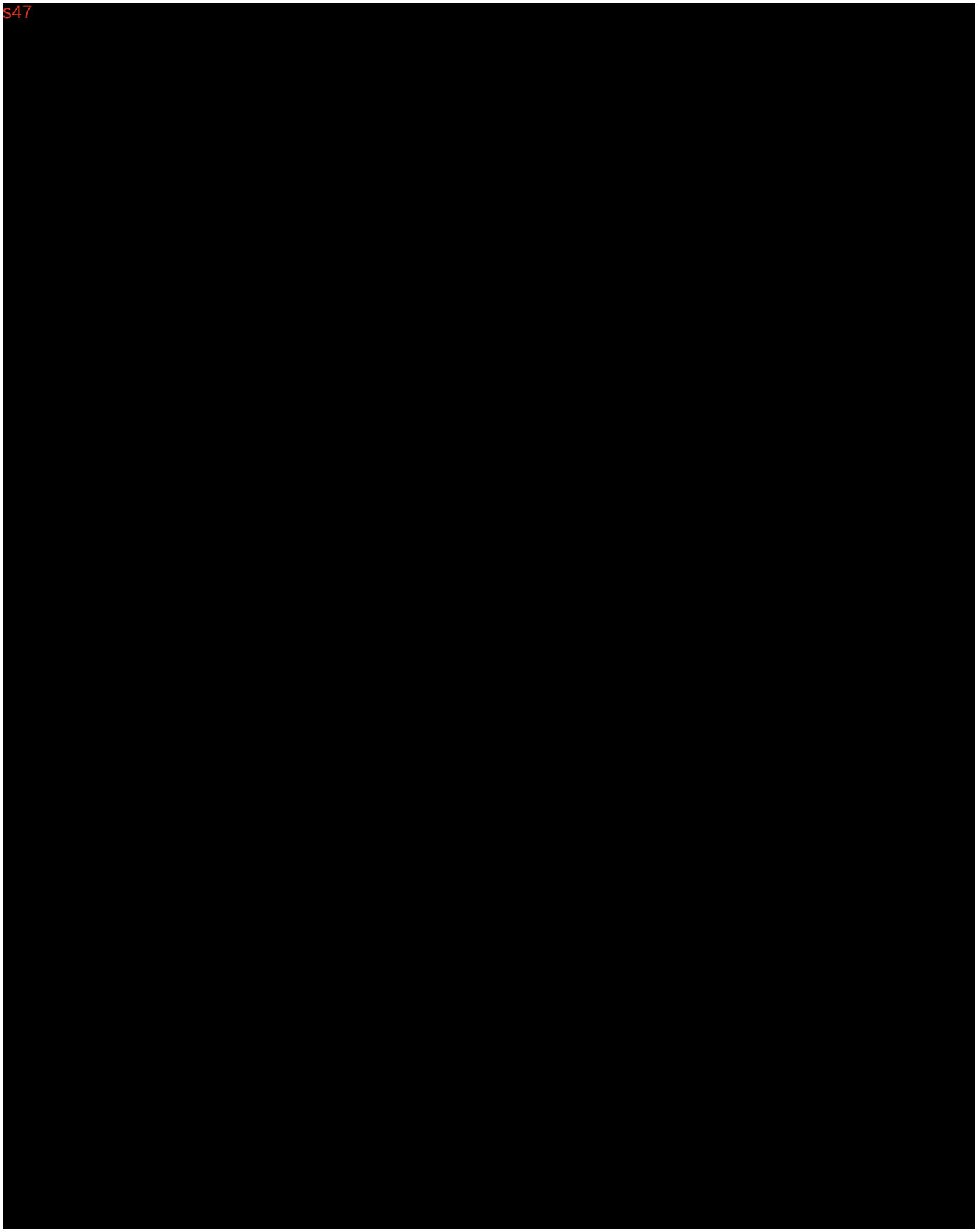

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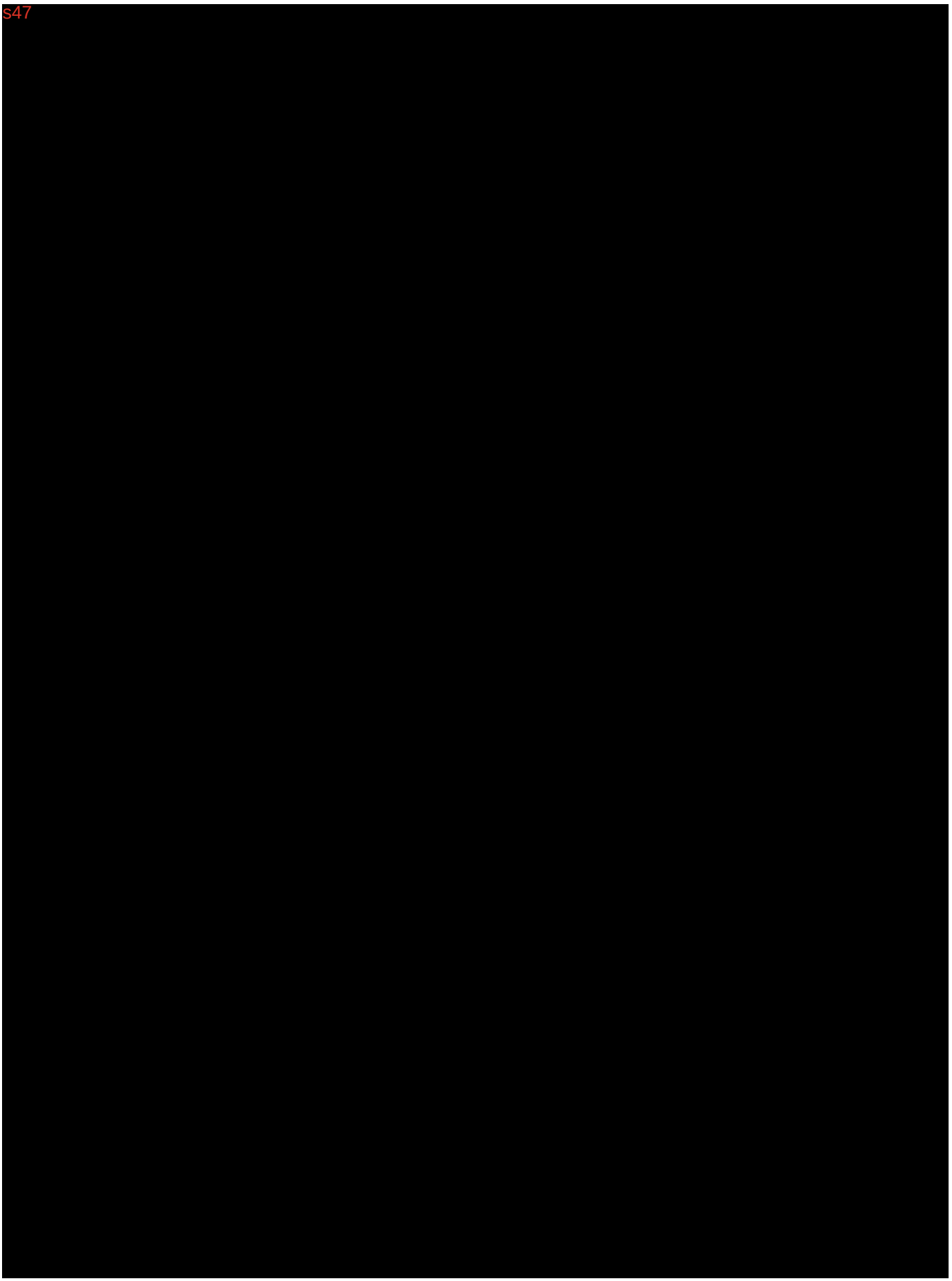

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3. REPEAT-DOSE TOXICITY

A single study in NZW rabbit examining the toxicity of repeated doses of SARS-CoV-2 rS (NVX-CoV2373) with the adjuvant, Matrix-M1 was submitted (Table 3.1). Since this submitted study did not include an adjuvant only test group, additional supporting studies (in SD rats and NZW rabbits) non-SARS-CoV-2 antigens and Matrix M1 were provided for evaluation of the toxicity for the adjuvant, Matrix-M1. All the studies were GLP–compliant. Studies 37348 TSR, 161014 and 2088-13549 are not evaluated due to the absence of test item concentrations details or the lack of adjuvant only test groups.

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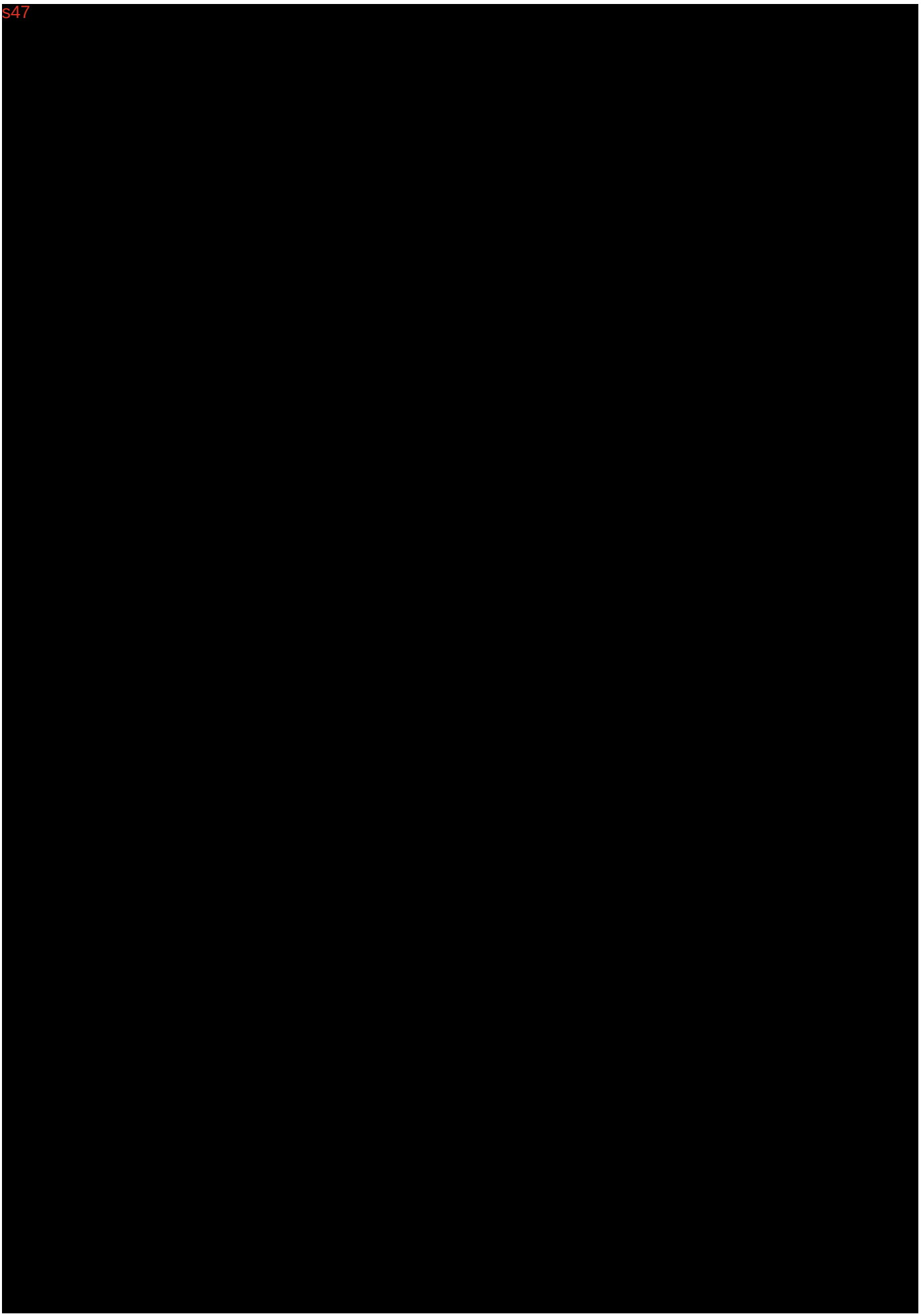

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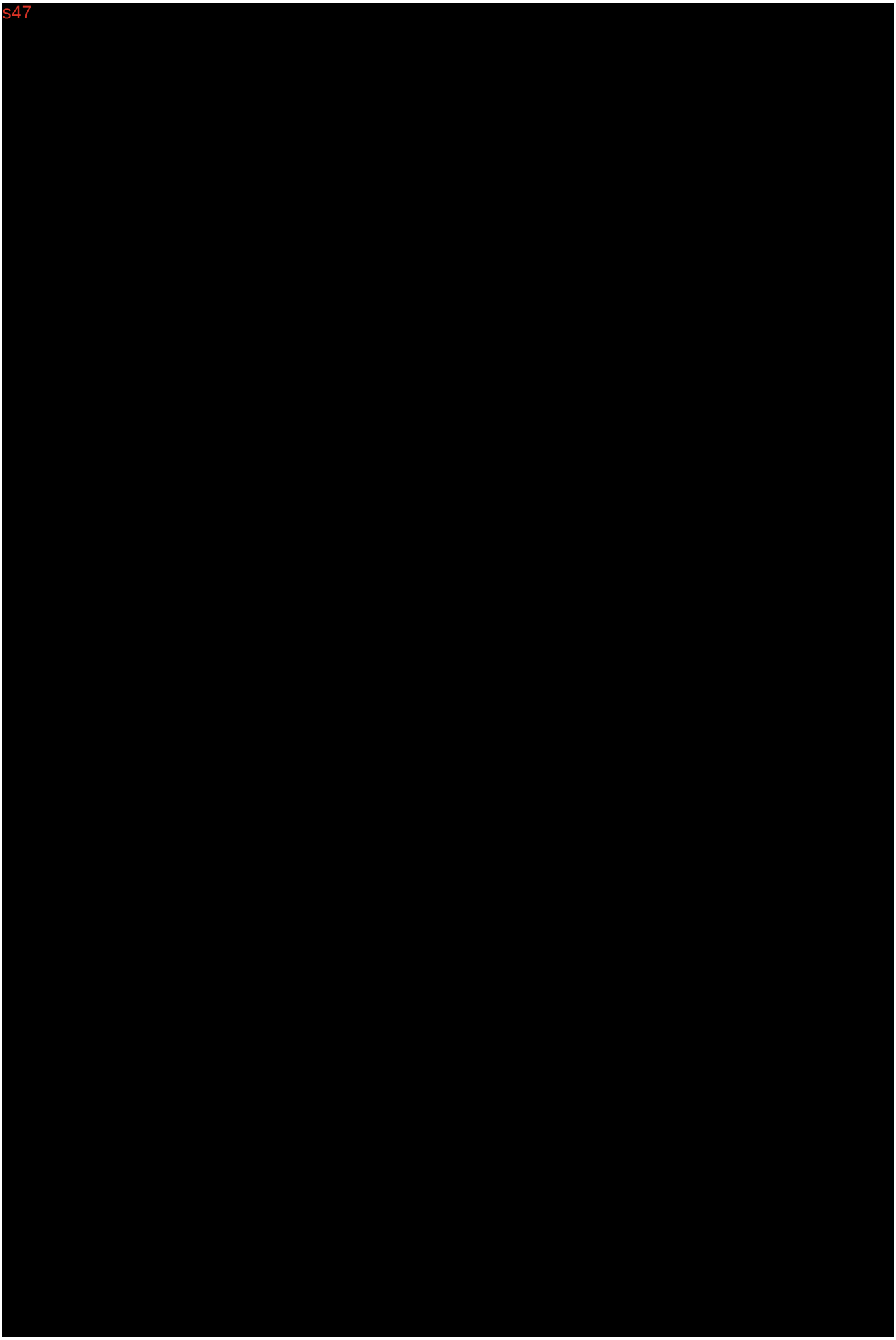

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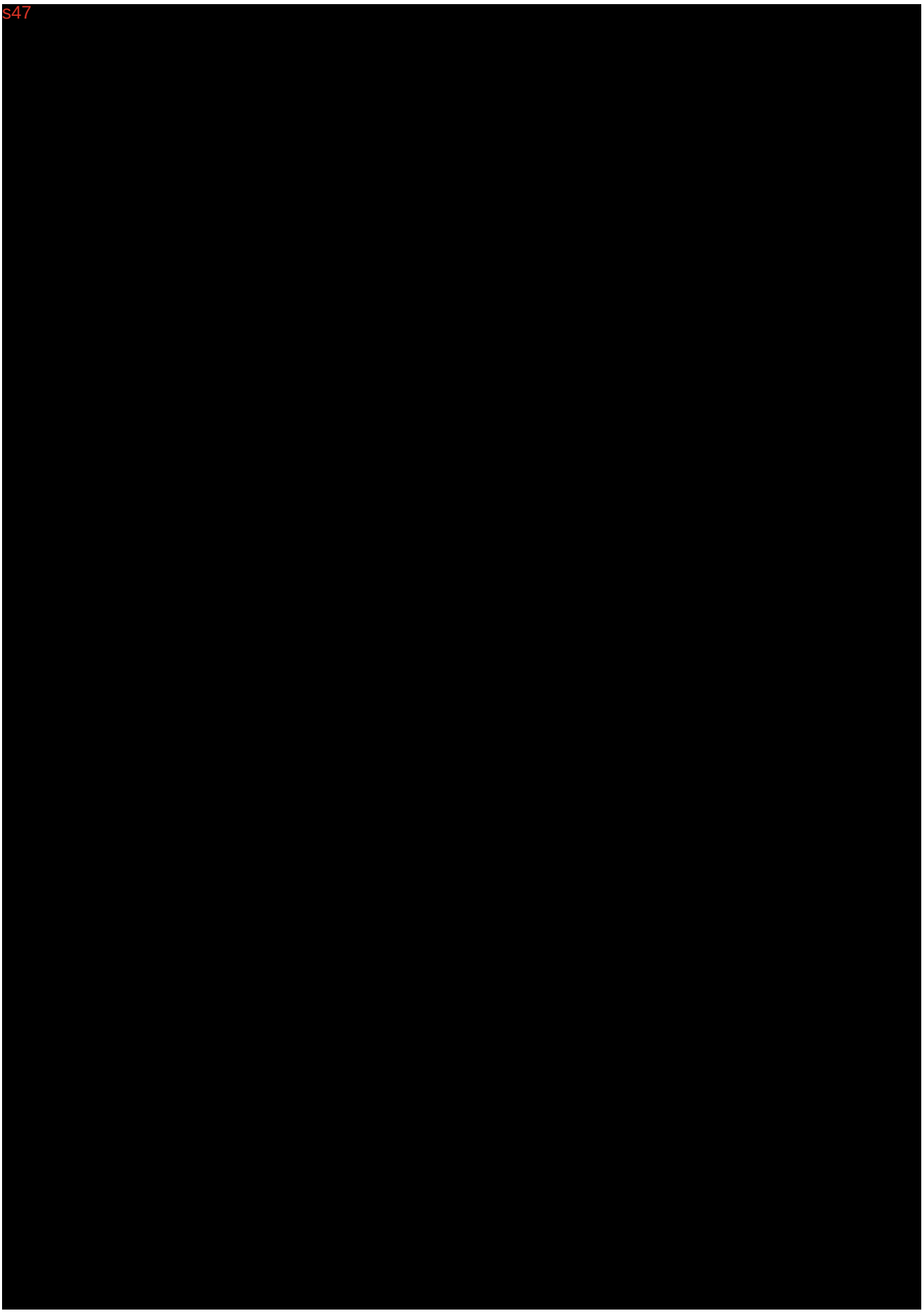

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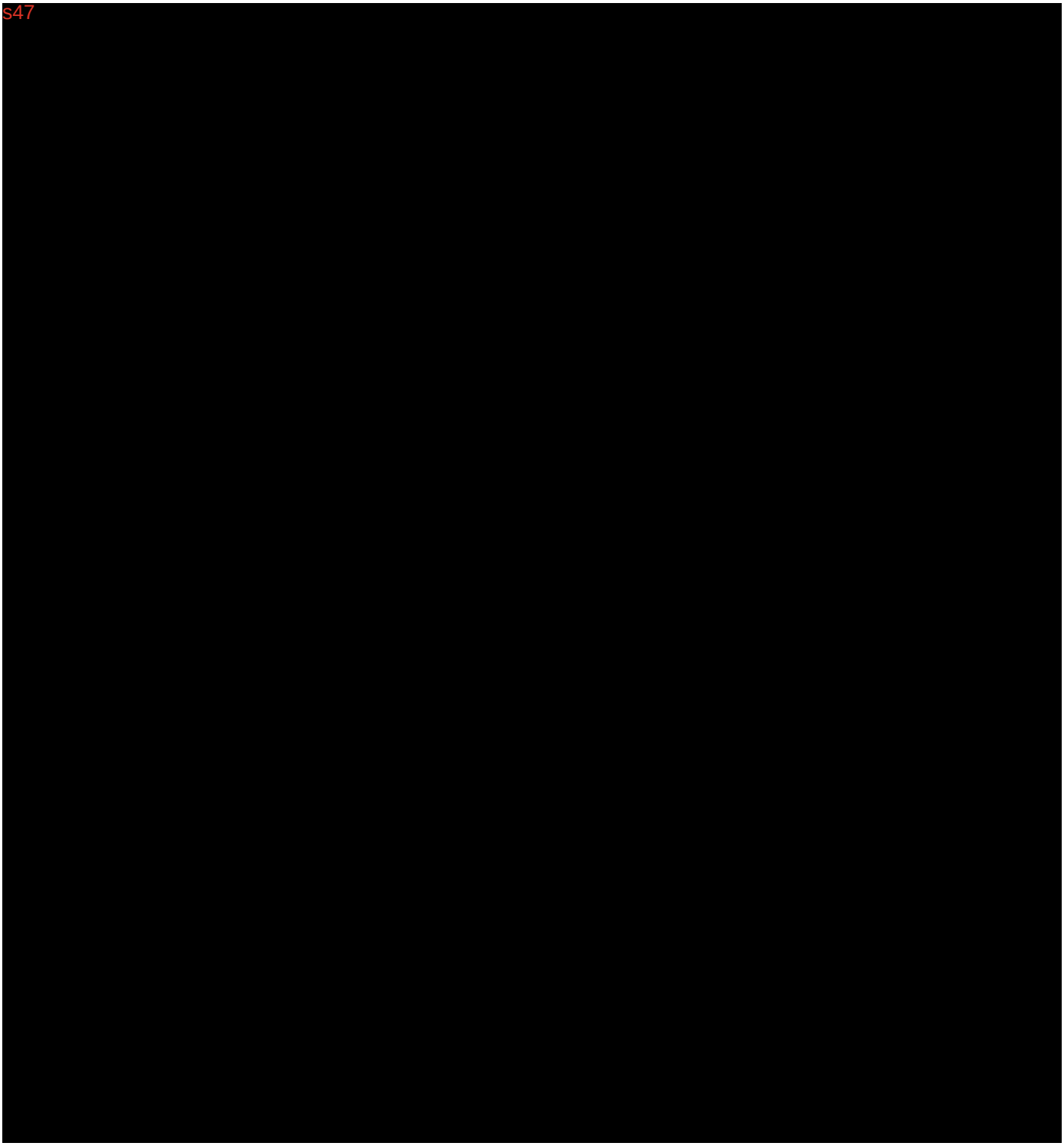

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4. GENOTOXICITY

The submitted genotoxicity studies on Matrix-M1 included two non–GLP and two GLP–compliant studies conducted at the same laboratory. The *in vitro* screening genotoxicity tests were negative for Matrix–M1.

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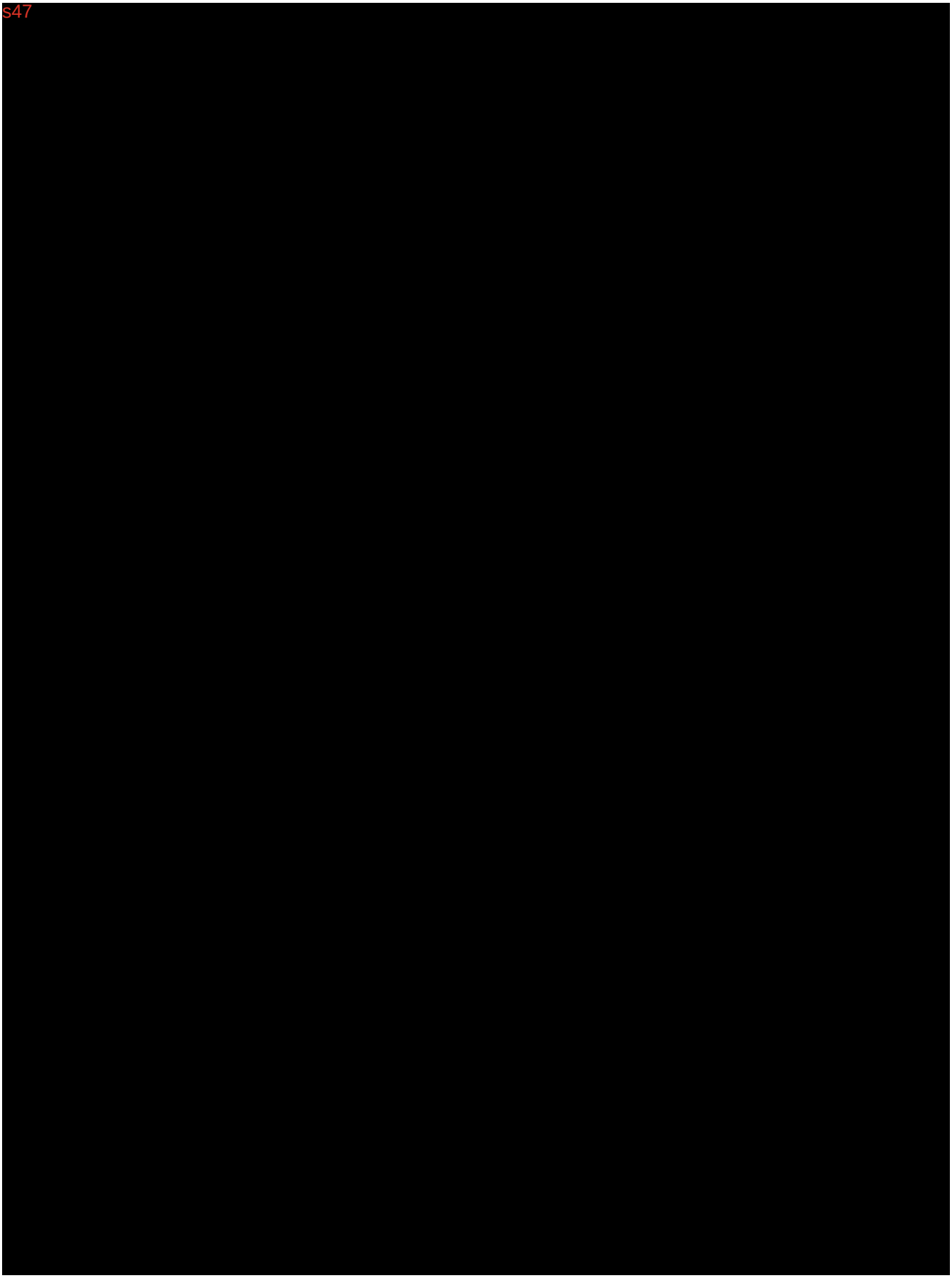

5. REPRODUCTIVE AND DEVELOPMENTAL STUDIES

Non-GLP pilot study with SARS-CoV-2 rS + Matrix-M1 was conducted first to confirm the immunogenicity of the intended dose and formulation in SD rats. A single GLP–compliant reproductive and developmental study in SD rats was conducted with SARS-CoV-2 rS + Matrix-M1 and Matrix-M1 only, which is evaluated below. The Sponsor has stated that "*no male fertility studies are planned given no adverse observations in male reproductive organs were observed in the GLP repeat-dose toxicology study*" (Module 2.4, Nonclinical overview, Section 2.4.4.5, Pg. 32).

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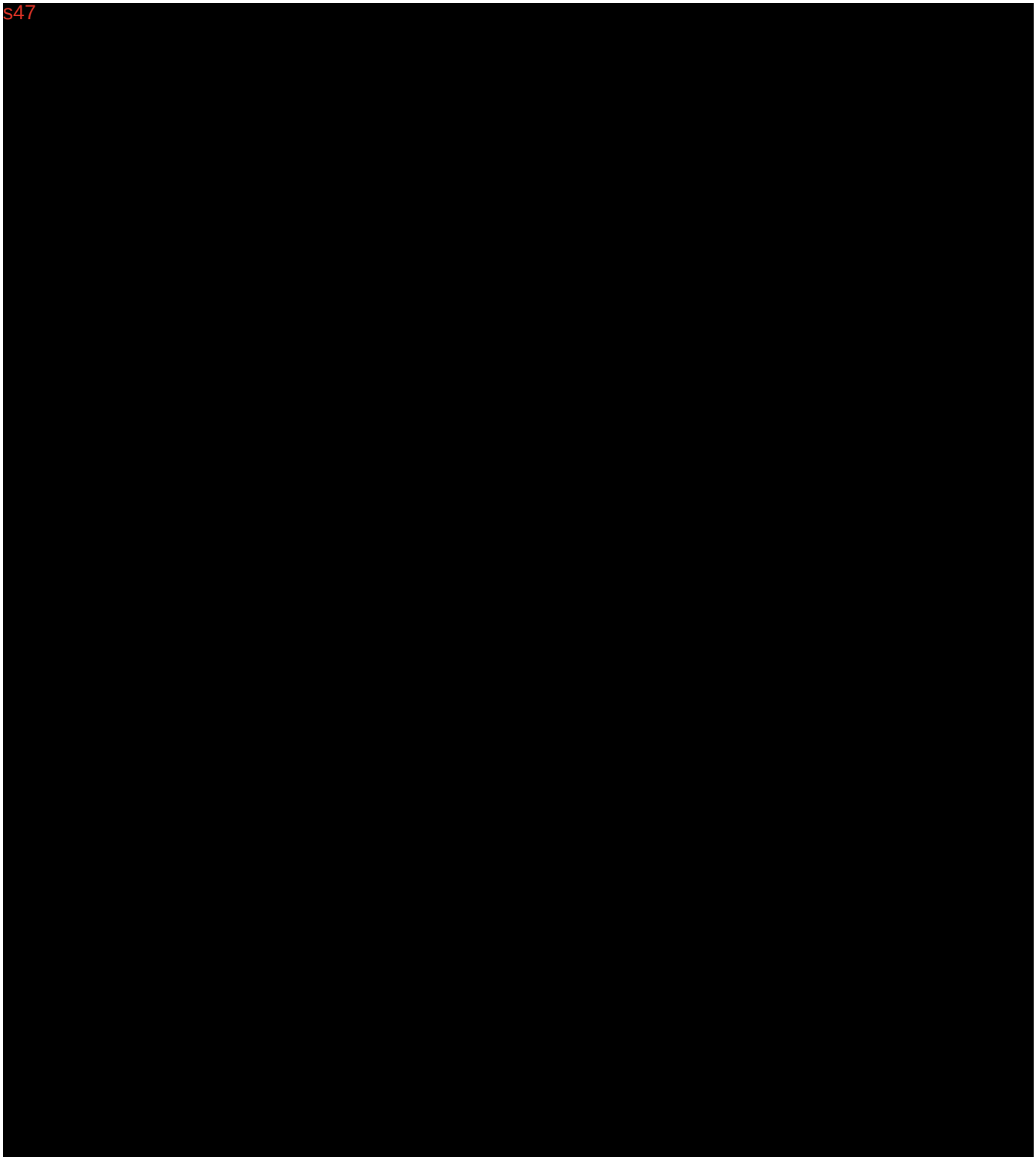

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6. LOCAL TOLERANCE

Separate local tolerance studies were not submitted. Local tolerance was evaluated in the repeat-dose toxicity study with SARS-CoV-2 rS +100 µg/mL Matrix-M1 in rabbits and local tolerance of Matrix-M1 was assessed in repeat–dose toxicity studies with other vaccines in animals treated with the adjuvant, Matrix-M1 only (Section 3).

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1. SUMMARY INFORMATION ON THE FINISHED PRODUCT (FINAL LOT)

Trade name:	**Nuvaxovid**
International non-proprietary Name / Ph. Eur. name / common name:	COVID-19 Vaccine (recombinant, adjuvanted)
Finished product (final lot) batch number:	4301MF004
Final bulk batch number:	4301MF004
Label Strength: SARS-CoV-2 rS Drug Product 10 µg/mL with 100 µg/mL Matrix-M Adjuvant	Administration: 0.5 mL / dose 10 doses per vial
Storage temperature:	2 to 8 °C
Total number of containers in this batch[1]:	s47 [redacted]
Number of doses per container:	10
Composition (antigen concentration)/ volume of single human dose:	One dose (0.5 mL) contains 5 micrograms of the of SARS-CoV-2 spike protein and is adjuvanted with Matrix-M.
Date of manufacture:	22-Nov-2021
Date of Expiry:	Apr 2022
Marketing authorisation number (member state / EU / UK) issued by:	Therapeutics Goods Administration Reference: ARTG No. 355139
Name and address of manufacturer:	Serum Institute of India Pvt. LTD s22 [redacted]
Name and address of Marketing Authorisation Holder if different:	NOVAVAX CZ a.s. s22 [redacted]
Name and Address of Australia Sponsor:	Biocelect Pty Ltd s22 [redacted]

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Finished Product	4301MF004	22 Nov 2021	s47 [redacted]	TBD	Apr 2022
Final Bulk	4301MF004	22 Nov 2021		Nov 21	Apr 2022
Monovalent bulk (Bulk Drug Substance)[2]	s47 [redacted]	s47 [redacted]		s47 [redacted]	

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Matrix-A	s47				
Matrix-C					
s47					

[1] The quantity intended for release to the market

s47

[3] DOM is start date of the activity

PRODUCTION FLOW

s47

STARTING MATERIALS

INTERMEDIATE STAGES

FINISHED PRODUCT

2. STARTING MATERIALS

2.1. Working Cell Bank

2.1.1. Production information

Batch No	s47	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Precursor	**Batch**	**Release date**
Master Cell Bank	s47	

2.1.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Direct Inoculation USP <71> Ph. Eur. 2.6.1, ICH Q5D	On test: s47 Off test: s47	No growth	No growth
	Mycoplasma / Spiroplasma	s47	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Adventitious agents		s47	No evidence of adventitious viral agents	No evidence of adventitious viral agents
	Mycobacteria		s47	No presence of Mycobacteria	No presence of Mycobacteria
Identity	Identity s47		s47	*Spodoptera spp.*	*Spodoptera spp*
Functionality	s47				

2.2. Working Virus Bank

2.2.1. Production information

Batch No	s47	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Storage time and approved storage period		
Precursors	**Batch**	**Release date**
Master Virus Stock	s47	
Primary Virus Stock		
Working Cell Bank		
Master Cell Bank		

2.2.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Testing Performed on Harvest					
Contaminants	Mycoplasma / Spiroplasma	s47		No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Mycobacterium			No evidence of Mycobacterium	No evidence of Mycobacterium
	Adventitious Agents			No evidence of significant adventitious viral agent nucleic acid reads	No evidence of significant adventitious viral agent nucleic acid reads
Testing Performed on Working Virus Bank					
Quantity	Virus Titer	s47			
Contaminants	Sterility	Membrane Filtration USP <71> and Ph. Eur. 2.6.1	On test s47 Off test s47	No growth	No growth
Identity	Nucleotide Sequence Analysis	s47			
s47					

3. INTERMEDIATE STAGES

3.1. Monovalent Bulk[3)]

s47 [redacted]

3.1.1. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity			g
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	Date
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture method			
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	**Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47 consistent with Assay Control	s47 consistent with Assay Control
				s47	s47
	Residual DNA	s47		≤ 200 ng/mg total protein	3.6 ng/mg
	Residual Infectious Baculovirus	s47		None Detected s47	None detected
Identity	Identity	s47		Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration	s47		s47	s47
Potency	Relative Potency	s47		s47	s47

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Excipients	PS-80 Content	s47	s47	s47	s47
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47	s47	0 cfu/10mL***
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	Less than 1.00 EU/mL

s47

**s47

** s47

3.1.2. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity			G
Storage temperature			
Working Cell Bank Batch No		**Thawing Date**[5)]	s47
Working Virus Bank Batch No			

Manufacturing step	Date
s47	
s47	
s47	
s47	
s47	
s47	
s47	
s47	

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	**Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47	s47
				consistent with Assay Control	consistent with Assay Control
				s47	
	Residual DNA			≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Excipients	PS-80 Content	s47	s47	s47	s47
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12			0 cfu/10 mL***
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

s47

**s47

** s47

3.1.3. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No	**Thawing Date[5)]**	s47	
Working Virus Bank Batch No			
Manufacturing step	**Date**		
s47			
s47			
s47			
s47			
s47			
s47			
s47			
s47			

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.3.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR or Culture Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth	No growth
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control s47	s47 with Assay Control
	Residual DNA			≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				
Excipients	PS-80 Content			s47	s47

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47	s47	0 cfu/10mL*
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

s47

**Appeas47

** s47

3.2. Matrix-A[6)]

[6)] s47

3.2.1. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	s47
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Purity	Saponin Purity	s47	s47	s47	s47
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47	s47		s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.2. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Phosphatidylcholine (PC) Concentration	s47	s47	s47	
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.3. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.3.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur.		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Assay	Saponin Concentration	s47	s47	s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.4. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.4.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20	s47	Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or		7.0 - 7.4	7.1
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3. Matrix-C[7)]

s47

3.3.1. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.4. Final bulk vaccine

Batch No	4301MF004		
Manufacturing site	s47 [redacted]		
Date of manufacture (Sterile filtration)			
Date of blending			
Filling date			
Expiration Date			
Container type	Vial		
Number of containers filled[8)]	s47 [redacted]		
Storage temperature	2 to 8 °C		
Component	**Batch No(s)**	**Quantity**	
SARS-CoV-2 rS Bulk Drug Substance	s47 [redacted]	s47 [redacted]	g
Matrix-A			g
Matrix-C			g

[8)] Quantity of vials filled after pulling all necessary samples = quantity intended for packaging as the next manufacturing step

4. BATCH OF FINISHED PRODUCT (FINAL LOT)

4.1. Production information

Finished Product Batch No	4301MF004		
Manufacturing site	Serum, Manjari		
Number of containers packed[9)]	s47 [redacted]		
Packaging date	29 Jan to 01 Feb 2022		
Drug Product Visual Inspection Information			
Number of Vials Inspected	s47 [redacted]	**Number of Vials Rejected:**	s47 [redacted]

[9)] Quantity of vials packed after pulling all necessary samples

4.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2.	s47 [redacted]	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Free from visible particles	*Colorless, clear liquid, free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3	s47 [redacted]	6.8 – 7.6	7.2
	Osmolality	Freezing Point Depression USP <785> Ph. Eur. 2.2.35	s47 [redacted]	NLT 240 mOsm/kg	576
Identity	Identity	s47 [redacted]	s47 [redacted]	Identity Confirmed	Complies
Quantity	Total Protein Concentration	s47 [redacted]	s47 [redacted]	s47 [redacted]	
Potency	Relative Potency	s47 [redacted]	s47 [redacted]		
Excipients	Matrix-A Content	s47 [redacted]	s47 [redacted]		
	Matrix-C Content		s47 [redacted]		

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Membrane Filtration USP <71> Ph. Eur. 2.6.1	s47 [redacted] s47 [redacted]	No Growth	No evidence of microbial growth observed
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47 [redacted]	s47 [redacted]	< 1.00 EU/mL
Extractable Volume	Dose Delivery	USP <1>, <697> and Ph. Eur. 2.9.17	s47 [redacted]	**For single dose:** The content of each container, not less than 0.5 mL and not less than the sum of the nominal volume of the containers taken collectively. **For multidose container:** The volume should be such that each syringe delivers not less than stated doses.	Total number of doses recovered = 10

*Descriptive language used per current method at Serum. Testing using Ph. Eur method pending.

5. CERTIFICATION

I herewith certify that COVID-19 Vaccine (recombinant, adjuvanted) batch N° 4301MF004 was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

Serum Quality Approver Printed Name:	s22 [redacted]
Serum Quality Approver Signature/Date:	s22 [redacted] s47 [redacted] | 0 :11 EST Signer Name: s22 [redacted] Signing Reason: I approve this document Signing Time: s47 [redacted] s22 [redacted]
Novavax Quality Approver Printed Name:	s22 [redacted]
Novavax Quality Approver Signature/Date:	DocuSigned by: s22 [redacted] s47 [redacted] | 0 :15 EST Signer Name: s22 [redacted] Signing Reason: I approve this document Signing Time: s47 [redacted] s22 [redacted]

1. SUMMARY INFORMATION ON THE FINISHED PRODUCT (FINAL LOT)

Trade name:	**Nuvaxovid**
International non-proprietary Name / Ph. Eur. name / common name:	COVID-19 Vaccine (recombinant, adjuvanted)
Finished product (final lot) batch number:	4301MF005
Final bulk batch number:	4301MF005
Label Strength: SARS-CoV-2 rS Drug Product 10 µg/mL with 100 µg/mL Matrix-M Adjuvant	Administration: 0.5 mL / dose 10 doses per vial
Storage temperature:	2 to 8 °C
Total number of containers in this batch[1]:	s47 [redacted]
Number of doses per container:	10
Composition (antigen concentration)/ volume of single human dose:	One dose (0.5 mL) contains 5 micrograms of the of SARS-CoV-2 spike protein and is adjuvanted with Matrix-M.
Date of manufacture:	24-Nov-2021
Date of Expiry:	Apr 2022
Marketing authorisation number (member state / EU / UK) issued by:	Therapeutics Goods Administration Reference: ARTG No. 355139
Name and address of manufacturer:	Serum Institute of India Pvt. LTD s22 [redacted]
Name and address of Marketing Authorisation Holder if different:	NOVAVAX CZ a.s. s22 [redacted]
Name and Address of Australia Sponsor:	Biocelect Pty Ltd s22 [redacted]

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Finished Product	4301MF005	Nov 2021	s47 [redacted]	07 Feb 2022	Apr 2022
Final Bulk	4301MF005	Nov 2021		07 Feb 2022	Apr 2022
Monovalent bulk (Bulk Drug Substance)[2]	s47 [redacted]	s47 [redacted]		s47 [redacted]	
Matrix-A[2]	s47 [redacted]			s47 [redacted]	

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
	s47				
Matrix-C[2)]					
s47					

[1)] The quantity intended for release to the market

s47

PRODUCTION FLOW

s47

STARTING MATERIALS

INTERMEDIATE STAGES

FINISHED PRODUCT

2. STARTING MATERIALS

2.1. Working Cell Bank

2.1.1. Production information

Batch No	s47	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Precursor	**Batch**	**Release date**
Master Cell Bank	s47	s47

2.1.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Direct Inoculation USP <71> Ph. Eur. 2.6.1, ICH Q5D	On test: s47 Off test: s47	No growth	No growth
	Mycoplasma / Spiroplasma	s47	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Adventitious agents		s47	No evidence of adventitious viral agents	No evidence of adventitious viral agents
	Mycobacteria		s47	No presence of Mycobacteria	No presence of Mycobacteria
Identity	Identity s47		s47	*Spodoptera spp.*	*Spodoptera spp*
Functionality	s47				

2.2. Working Virus Bank

2.2.1. Production information

Batch No	s47	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Storage time and approved storage period		
Precursors	**Batch**	**Release date**
Master Virus Stock	s47	
Primary Virus Stock		
Working Cell Bank		
Master Cell Bank		

2.2.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Testing Performed on Harvest					
Contaminants	Mycoplasma / Spiroplasma	s47		No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Mycobacterium			No evidence of Mycobacterium	No evidence of Mycobacterium
	Adventitious Agents			No evidence of significant adventitious viral agent nucleic acid reads	No evidence of significant adventitious viral agent nucleic acid reads
Testing Performed on Working Virus Bank					
Quantity	Virus Titer	s47			
Contaminants	Sterility	Membrane Filtration USP <71> and Ph. Eur. 2.6.1	On test s47 Off test s47	No growth	No growth
Identity	Nucleotide Sequence Analysis	s47			
s47					

3. INTERMEDIATE STAGES

3.1. Monovalent Bulk[3)]

s47 [redacted]

3.1.1. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity			g
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	**Date**
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR or Culture Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth	No growth
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2	s47	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	**Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3	s47	6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 consistent with Assay Control s47	s47 band consistent with Assay Control
	Residual DNA	s47	s47	≤ 200 ng/mg total protein	< 3.2 ng/mg
	Residual Infectious Baculovirus	s47	s47	None Detected s47	None detected
Identity	Identity	s47	s47	Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration	s47	s47	s47	s47
Potency	Relative Potency	s47	s47	s47	s47
Excipients	PS-80 Content	s47	s47	s47	s47
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47	s47	0 cfu/10mL***

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	Less than 1.00 EU/mL

s47

**s47

** s47

3.1.2. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47
Working Virus Bank Batch No			

Manufacturing step	Date
s47	
s47	
s47	
s47	
s47	
s47	
s47	
s47	

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	** Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control	s47 consistent with Assay Control
				s47	
	Residual DNA	s47		≤ 200 ng/mg total protein	3.3 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Excipients	PS-80 Content	s47	s47	s47	s47
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12			0 cfu/10 mL***
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

s47

**s47

** s47

3.1.3. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No		**Thawing Date**[5)]	s47
Working Virus Bank Batch No			

Manufacturing step	Date
s47	
s47	
s47	
s47	
s47	
s47	
s47	
s47	

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.3.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility*	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	** Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control	s47 band consistent with Assay Control
				s47	
	Residual DNA	s47		≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency			s47	

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Excipients	PS-80 Content	s47	s47	s47	s47
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12			0 cfu/10mL***
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

s47

**s47

** s47

3.2. Matrix-A[6)]

s47

3.2.1. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	s47
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Impurity	s47	s47	s47	s47	
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.1
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC) Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61> Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL ≤ 10 CFU/100 mL	0 cfu/100 mL TAMC 0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.2. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Cholesterol Concentration	s47	s47	s47	
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.3. Production information

Matrix A	
Batch No	s47
Manufacturing site	
Date of manufacture	
Quantity	
Expiration date	
Storage temperature	

3.2.3.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Identification	Identity	s47	s47	Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3. Matrix-C[7)]

s47

3.3.1. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47			s47	
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3.2. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.4. Final bulk vaccine

Batch No	4301MF005		
Manufacturing site	s47 [redacted]		
Date of manufacture (Sterile filtration)			
Date of blending			
Filling date			
Expiration Date			
Container type	Vial		
Number of containers filled[8)]	s47 [redacted]		
Storage temperature	2 to 8 °C		
Component	**Batch No(s)**	**Quantity**	
SARS-CoV-2 rS Bulk Drug Substance	s47 [redacted]	s47 [redacted]	kg
Matrix-A			g
Matrix-C			g

[8)] Quantity of vials filled after pulling all necessary samples = quantity intended for packaging as the next manufacturing step

4. BATCH OF FINISHED PRODUCT (FINAL LOT)

4.1. Production information

Finished Product Batch No	4301MF005		
Manufacturing site	Serum, Manjari		
Number of containers packed[9)]	s47 [redacted]		
Packaging date	02 Feb 2022 to 04 Feb 2022		
Drug Product Visual Inspection Information			
Number of Vials Inspected	s47 [redacted]	**Number of Vials Rejected:**	s47 [redacted]

[9)] Quantity of vials packed after pulling all necessary samples

4.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2.	s47 [redacted]	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Free from visible particles	*Colorless, clear liquid, free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3	s47 [redacted]	6.8 – 7.6	7.2
	Osmolality	Freezing Point Depression USP <785> Ph. Eur. 2.2.35	s47 [redacted]	NLT 240 mOsm/kg	590
Identity	Identity	s47 [redacted]	s47 [redacted]	Identity Confirmed	Complies
Quantity	Total Protein Concentration		s47 [redacted]	s47 [redacted]	
Potency	Relative Potency		s47 [redacted]		
Excipients	Matrix-A Content		s47 [redacted]		
	Matrix-C Content		s47 [redacted]		

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Membrane Filtration USP <71> Ph. Eur. 2.6.1	On test: s47 Off Test: s47	No Growth	No evidence of microbial growth observed
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	< 1.00 EU/mL
Extractable Volume	Dose Delivery	USP <1>, <697> and Ph. Eur. 2.9.17	s47	**For single dose:** The content of each container, not less than 0.5 mL and not less than the sum of the nominal volume of the containers taken collectively. **For multidose container:** The volume should be such that each syringe delivers not less than stated doses.	Total number of doses recovered = 10

*Descriptive language used per current method at Serum. Testing using Ph. Eur. Method pending.

5. CERTIFICATION

I herewith certify that COVID-19 Vaccine (recombinant, adjuvanted) batch N° 4301MF005 was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

Serum Quality Approver Printed Name:	s22
Serum Quality Approver Signature/Date:	s22 Signer Name: s22 Signing Reason: I approve this document Signing Time: s47 s22 s47 | 0 :14 EST
Novavax Quality Approver Printed Name:	s22 Signed by:
Novavax Quality Approver Signature/Date:	s22 Signer Name: s22 Signing Reason: I approve this document Signing Time: s47 s22 s47 | :58 EST

1. SUMMARY INFORMATION ON THE FINISHED PRODUCT (FINAL LOT)

Trade name:	**Nuvaxovid**
International non-proprietary Name / Ph. Eur. name / common name:	COVID-19 Vaccine (recombinant, adjuvanted)
Finished product (final lot) batch number:	4302MF011
Final bulk batch number:	4302MF011
Label Strength: SARS-CoV-2 rS Drug Product 10 µg/mL with 100 µg/mL Matrix-M Adjuvant	Administration: 0.5 mL / dose 10 doses per vial
Storage temperature:	2 to 8 °C
Total number of containers in this batch[1]:	s47 [redacted]
Number of doses per container:	10
Composition (antigen concentration)/ volume of single human dose:	One dose (0.5 mL) contains 5 micrograms of the of SARS-CoV-2 spike protein and is adjuvanted with Matrix-M.
Date of manufacture:	09 Feb 2022
Date of Expiry:	Jul 2022
Marketing authorisation number (member state / EU / UK) issued by:	Therapeutics Goods Administration Reference: ARTG No. 355139
Name and address of manufacturer:	Serum Institute of India Pvt. LTD s22 [redacted]
Name and address of Marketing Authorisation Holder if different:	NOVAVAX CZ a.s. s22 [redacted]
Name and Address of Australia Sponsor:	Biocelect Pty Ltd s22 [redacted]

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Finished Product	4302MF011	09 Feb 2022	s47 [redacted]	27 Apr 2022	Jul 2022
Final Bulk	4302MF011	09 Feb 2022		09 Mar 2022	Jul 2022
Monovalent bulk (Bulk Drug Substance)[2]	s47 [redacted]			s47 [redacted]	

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Matrix-A[2)]	s47				
Matrix-C[2)]					
s47					

[1)] The quantity intended for release to the market

s47

PRODUCTION FLOW

s47

STARTING MATERIALS

INTERMEDIATE STAGES

FINISHED PRODUCT

2. STARTING MATERIALS

2.1. Working Cell Bank

2.1.1. Production information

Batch No	s47		
Manufacturing site			
Date of manufacture			
Storage temperature			
Volume			
Precursor	**Batch**	**Release date**	
Master Cell Bank	s47	s47	

2.1.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Direct Inoculation USP <71> Ph. Eur. 2.6.1, ICH Q5D	On test: s47 Off test: s47	No growth	No growth
	Mycoplasma / Spiroplasma	s47	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Adventitious agents		s47	No evidence of adventitious viral agents	No evidence of adventitious viral agents
	Mycobacteria		s47	No presence of Mycobacteria	No presence of Mycobacteria
Identity	Identity s47		s47	*Spodoptera spp.*	*Spodoptera spp*
Functionality	s47				

2.2. Working Virus Bank

2.2.1. Production information

Batch No	s47	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Storage time and approved storage period		
Precursors	**Batch**	**Release date**
Master Virus Stock	s47	
Primary Virus Stock		
Working Cell Bank		
Master Cell Bank		

2.2.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Testing Performed on Harvest					
Contaminants	Mycoplasma / Spiroplasma	s47		No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Mycobacterium			No evidence of Mycobacterium	No evidence of Mycobacterium
	Adventitious Agents			No evidence of significant adventitious viral agent nucleic acid reads	No evidence of significant adventitious viral agent nucleic acid reads
Testing Performed on Working Virus Bank					
Quantity	Virus Titer	s47			
Contaminants	Sterility	Membrane Filtration USP <71> and Ph. Eur. 2.6.1	On test: s47 Off test: s47	No growth	No growth
Identity	Nucleotide Sequence Analysis	s47			

3. INTERMEDIATE STAGES

3.1. Monovalent Bulk[3)]

s47 [redacted]

3.1.1. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity			g
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	**Date**
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR or Culture Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth	No growth
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2	s47	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47 consistent with Assay Control	s47 band consistent with Assay Control
				s47	
	Residual DNA	s47		≤ 200 ng/mg total protein	3.3 ng/mg
	Residual Infectious Baculovirus	s47		None Detected s47	None detected
Identity	Identity	s47		Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration	s47		s47	s47
Potency	Relative Potency	s47		s47	s47
Excipients	PS-80 Content	s47		s47	s47

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47	s47	0 cfu/100mL
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			< 1.00 EU/mL

[1] s47

3.1.2. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4]			
Expiration Date			
Quantity			g
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5]**	s47
Working Virus Bank Batch No			

Manufacturing step	Date
s47	
s47	
s47	
s47	
s47	
s47	
s47	
s47	

[4] End of manufacturing
[5] Start of manufacturing

3.1.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control	s47 consistent with Assay Control
				s47	
	Residual DNA			≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				
Excipients	PS-80 Content				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47 [redacted]		0 cfu/100 mL
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

[1] s47 [redacted]

3.1.3. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	Date
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.3.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control	s47 band consistent with Assay Control
				s47	
	Residual DNA			≤ 200 ng/mg total protein	3.5 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				
Excipients	PS-80 Content				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47 [redacted]		0 cfu/100mL
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			< 1.00 EU/mL

s47 [redacted]

3.1.4. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity			g
Storage temperature			
Working Cell Bank Batch No		**Thawing Date**[5)]	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	Date
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.4.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
		Culture Method			
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.3
Purity/Impurities	Purity	s47		s47 band consistent with Assay Control	s47 band consistent with Assay Control
				s47	
	Residual DNA			≤ 200 ng/mg total protein	3.7 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				
Excipients	PS-80 Content			s47	s47

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47		1 cfu/100mL
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			Less than 1.00 EU/mL

3.2. Matrix-A[6]

s47

3.2.1. Production information

Matrix A		
Batch No	s47	
Manufacturing site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.2.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B4
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	s47
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Particle Size	s47	s47	s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3. Matrix-C[7)]

s47

3.3.1. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Conforms
Identification	Identity	s47		Identity consistent with reference	Conforms
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Phosphatidylcholine (PC) Concentration	s47	s47	s47	
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3.2. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B6
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Practically free from foreign visible particles
Identification	Identity	s47		Identity consistent with reference	Identity consistent

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
			s47		with reference
Assay	Saponin Concentration	s47		s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.4. Final bulk vaccine

Batch No	4302MF011		
Manufacturing site	s47 [redacted]		
Date of manufacture (Sterile filtration)			
Date of blending			
Filling date			
Expiration Date			
Container type	Vial		
Number of containers filled[8)]	s47 [redacted]		
Storage temperature	2 to 8 °C		
Component	**Batch No(s)**	**Quantity**	
SARS-CoV-2 rS Bulk Drug Substance	s47 [redacted]	s47 [redacted]	kg
Matrix-A			g
Matrix-C			g

[8)] Quantity of vials filled after pulling all necessary samples = quantity intended for packaging as the next manufacturing step

4. BATCH OF FINISHED PRODUCT (FINAL LOT)

4.1. Production information

Finished Product Batch No	4302MF011		
Manufacturing site	Serum, Manjari		
Number of containers packed[9)]	s47		
Packaging date	26 Mar to 27 Mar 2022 & 30 Mar to 01Apr 2022		
Drug Product Visual Inspection Information			
Number of Vials Inspected	s47	**Number of Vials Rejected:**	s47

[9)] Quantity of vials packed after pulling all necessary samples

4.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2.	s47	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Free from visible particles	*Colorless, clear liquid, free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3	s47	6.8 – 7.6	7.2
	Osmolality	Freezing Point Depression USP <785> Ph. Eur. 2.2.35	s47	NLT 240 mOsm/kg	591 mOsm/kg
Identity	Identity	s47	s47	Identity Confirmed	Complies
Quantity	Total Protein Concentration	s47	s47	s47	
Potency	Relative Potency	s47	s47		
Excipients	Matrix-A Content	s47	s47		
	Matrix-C Content		s47		
Contaminants	Sterility	Membrane Filtration USP <71> Ph. Eur. 2.6.1	On test: s47 Off test: s47	No Growth	No evidence of microbial growth found

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	< 1.00 EU/mL
Extractable Volume	Dose Delivery	USP <1>, <697> and Ph. Eur. 2.9.17	s47	**For single dose:** The content of each container, not less than 0.5 mL and not less than the sum of the nominal volume of the containers taken collectively. **For multidose container:** The volume should be such that each syringe delivers not less than stated doses.	Total Number of Doses Recovered = 10

*Descriptive language used per current method at Serum. Testing using Ph. Eur. Method pending.

5. CERTIFICATION

I herewith certify that COVID-19 Vaccine (recombinant, adjuvanted) batch N° 4302MF011 was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

Serum Quality Approver Printed Name:	s22
Serum Quality Approver Signature/Date:	DocuSigned by: s22 s47 | 2 :10 EDT Signer Name s22
Novavax Quality Approver Printed Name:	s22 s47
Novavax Quality Approver Signature/Date:	s22 DocuSigned by: s22 Signer Name: s22 s47 | 18:08 Signing Reason: I approve this document Signing Time: s47 s22

1. SUMMARY INFORMATION ON THE FINISHED PRODUCT (FINAL LOT)

Trade name:	**Nuvaxovid**
International non-proprietary Name / Ph. Eur. name / common name:	COVID-19 Vaccine (recombinant, adjuvanted)
Finished product (final lot) batch number:	4302MF021
Final bulk batch number:	4302MF021
Label Strength: SARS-CoV-2 rS Drug Product 10 µg/mL with 100 µg/mL Matrix-M Adjuvant	Administration: 0.5 mL / dose 10 doses per vial
Storage temperature:	2 to 8 °C
Total number of containers in this batch[1]:	s47 [redacted]
Number of doses per container:	10
Composition (antigen concentration)/ volume of single human dose:	One dose (0.5 mL) contains 5 micrograms of the of SARS-CoV-2 spike protein and is adjuvanted with Matrix-M.
Date of manufacture:	18 May 2022
Date of Expiry:	Jan 2023
Marketing authorisation number (member state / EU / UK) issued by:	Therapeutics Goods Administration Reference: ARTG No. 355139
Name and address of manufacturer:	Serum Institute of India Pvt. LTD s22 [redacted]
Name and address of Marketing Authorisation Holder if different:	NOVAVAX CZ a.s. s22 [redacted]
Name and Address of Australia Sponsor:	Biocelect Pty Ltd s22 [redacted]

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
Finished Product	4302MF021	18 May 2022	s47 [redacted]	01Jul 2022	Jan 2023
Final Bulk	4302MF021	18 May 2022		09 Jun 2022	Jan 2023
Monovalent bulk (Bulk Drug Substance)[2]	s47 [redacted]			s47 [redacted]	
Matrix-A[2]					

Genealogy	Batch No	Date of manufacture	Manufacturing site	Release date	Expiration date
	s47				
Matrix-C[2)]					
s47					

[1)] The quantity intended for release to the market

s47

PRODUCTION FLOW

s47

STARTING MATERIALS

INTERMEDIATE STAGES

FINISHED PRODUCT

2. STARTING MATERIALS

2.1. Working Cell Bank

2.1.1. Production information

Batch No	s47		
Manufacturing site			
Date of manufacture			
Storage temperature			
Volume			
Precursor	**Batch**	**Release date**	
Master Cell Bank	s47	s47	

2.1.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants	Sterility	Direct Inoculation USP <71> Ph. Eur. 2.6.1, ICH Q5D	On test: s47 Off test: s47	No growth	No growth
	Mycoplasma / Spiroplasma	s47	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Adventitious agents		s47	No evidence of adventitious viral agents	No evidence of adventitious viral agents
	Mycobacteria		s47	No presence of Mycobacteria	No presence of Mycobacteria
Identity	Identit s47		s47	*Spodoptera spp.*	*Spodoptera spp*
Functionality	s47				

2.2. Working Virus Bank

2.2.1. Production information

Batch No	s47 [redacted]	
Manufacturing site		
Date of manufacture		
Storage temperature		
Volume		
Storage time and approved storage period		
Precursors	**Batch**	**Release date**
Working Virus Stock	s47 [redacted]	
Master Virus Stock		
Primary Virus Stock		
Working Cell Bank		
Master Cell Bank		

2.2.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Testing Performed on Harvest					
Contaminants	Mycoplasma / Spiroplasma	s47 [redacted]		No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Mycobacterium			No evidence of Mycobacterium	No evidence of Mycobacterium
	Adventitious Agents			No evidence of significant adventitious viral agent nucleic acid reads	No evidence of significant adventitious viral agent nucleic acid reads
Testing Performed on Working Virus Bank					
Quantity	Virus Titer	s47 [redacted]			
Contaminants	Sterility	Membrane Filtration USP <71> and Ph. Eur. 2.6.1	On test: s47 [redacted] Off test: s47 [redacted]	No growth	No growth
Identity	Nucleotide Sequence Analysis	s47 [redacted]			

3. INTERMEDIATE STAGES

3.1. Monovalent Bulk[3)]

s47 [redacted]

3.1.1. Production information

Bulk Drug Substance Batch No	s47 [redacted]		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47 [redacted]
Working Virus Bank Batch No			

Manufacturing step	Date
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]
s47 [redacted]	[redacted]

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR or Culture Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth	No growth
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47 consistent with Assay Control	s47 consistent with Assay Control
				s47	
	Residual DNA	s47		≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus	s47		None Detected s47	None detected
Identity	Identity	s47		Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration	s47		s47	
Potency	Relative Potency	s47		s47	
Excipients	PS-80 Content	s47		s47	
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12		s47	0 cfu/100mL

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	1.47 EU/mL

s47

3.1.2. Production information

Bulk Drug Substance Batch No	s47		
Manufacturing site			
Date of manufacture[4)]			
Expiration Date			
Quantity		g	
Storage temperature			
Working Cell Bank Batch No		**Thawing Date[5)]**	s47
Working Virus Bank Batch No			

Manufacturing step	Date
s47	
s47	
s47	
s47	
s47	
s47	
s47	
s47	

[4)] End of manufacturing
[5)] Start of manufacturing

3.1.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Harvest)	Mycoplasma / Spiroplasma	PCR Method USP <63> Ph. Eur. 2.6.7	s47	No evidence of Mycoplasma or Spiroplasma	No evidence of Mycoplasma or Spiroplasma
	Sterility	Direct Inoculation USP <71> EP 2.6.1		No growth observed	No growth observed
	Adventitious Agents	s47		No evidence of adventitious viral agents	No evidence of adventitious viral agents
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2		Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles	*Colorless, clear liquid free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3		6.8 – 7.6	7.2
Purity/Impurities	Purity	s47		s47 consistent with Assay Control	s47 consistent with Assay Control
				s47	
	Residual DNA			≤ 200 ng/mg total protein	<3.2 ng/mg
	Residual Infectious Baculovirus			None Detected s47	None detected
Identity	Identity			Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration			s47	
Potency	Relative Potency				
Excipients	PS-80 Content				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Contaminants (Drug Substance)	Drug Substance Bioburden	Membrane Filtration USP <61> Ph. Eur. 2.6.12	s47		0 cfu/100 mL
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14			1.19 EU/mL

s47

3.2. Matrix-A[6)]

s47

3.2.1. Production information

Matrix A		
Batch No	s47	
Manufacturing site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.2.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Practically free from foreign visible particles
Identification	Identity	s47		Identity consistent with reference	Identity consistent with reference
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Purity	Saponin Purity	s47	s47	s47	
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.2.2. Production information

Matrix A		
Batch No	s47	
Manufacturing site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.2.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Practically free from foreign visible particles
Identification	Identity	s47		Identity consistent with reference	Identity consistent with reference

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Assay	Saponin Concentration	s47	s47	s47	
	Cholesterol Concentration				
	Phosphatidyl choline (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TAMC
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL TYMC
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3. Matrix-C[7)]

s47

3.3.1. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		
Date of manufacture		
Quantity		
Expiration date		
Storage temperature		

3.3.1.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Practically free from foreign visible particles
Identification	Identity	s47		Identity consistent with reference	Identity consistent with reference
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.2
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	<1 cfu/100 mL
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.3.2. Production information

Matrix C		
Batch No	s47	
Manufacturing Site		

Date of manufacture	s47	
Quantity		
Expiration date		
Storage temperature		

3.3.2.1. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
Appearance	Color	Appearance, Ph. Eur. 2.2.2	s47	B3 - B7 (Ph. Eur. reference solution)	B5
	Clarity	Appearance, Based on Ph. Eur. 2.2.1		Opalescent	Opalescent
	Visible Particles	Appearance, Based on Ph. Eur. 2.9.20		Practically free from foreign visible particles	Practically free from foreign visible particles
Identification	Identity	s47		Identity consistent with reference	Identity consistent with reference
Assay	Saponin Concentration			s47	
	Cholesterol Concentration				
	Phosphatidylcholine (PC) Concentration				
Impurity	s47				
Purity	Saponin Purity				
Property	pH	Ph. Eur. 2.2.3 or USP <791>		7.0 - 7.4	7.1
	Particle Size	s47		s47	
	s47				
Microbiological Tests	Total Aerobic Microbial Count (TAMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Total Combined Yeasts and Molds Count (TYMC)	Ph. Eur. 2.6.12 or USP<61>		≤ 10 CFU/100 mL	0 cfu/100 mL
	Endotoxin	Ph. Eur. 2.6.14 or USP<85> (kinetic)		s47	

3.4. Final bulk vaccine

Batch No	4302MF021		
Manufacturing site	s47		
Date of manufacture (Sterile filtration)			
Date of blending			
Filling date			
Expiration Date			
Container type	Vial		
Number of containers filled[8)]	s47		
Storage temperature	2 to 8 °C		
Component	**Batch No(s)**	**Quantity**	
SARS-CoV-2 rS Bulk Drug Substance	s47	s47	kg
Matrix-A			g
Matrix-C			g

[8)] Quantity of vials filled after pulling all necessary samples = quantity intended for packaging as the next manufacturing step

4. BATCH OF FINISHED PRODUCT (FINAL LOT)

4.1. Production information

Finished Product Batch No	4302MF021		
Manufacturing site	Serum, Manjari		
Number of containers packed[9)]	s47		
Packaging date	09 Jun to 11 Jun 2022		
Drug Product Visual Inspection Information			
Number of Vials Inspected	s47	**Number of Vials Rejected:**	s47

[9)] Quantity of vials packed after pulling all necessary samples

4.2. Testing information

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
General Tests	Appearance: Color, Clarity, Visible Particles	Visual Observation Ph. Eur. 2.2.1 and 2.2.2.	s47	Color: Colorless to intensity ≤ Standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Free from visible particles	*Colorless, clear liquid, free from visible particles
	pH	Potentiometric USP <791> Ph. Eur. 2.2.3	s47	6.8 – 7.6	7.2
	Osmolality	Freezing Point Depression USP <785> Ph. Eur. 2.2.35	s47	NLT 240 mOsm/kg	593 mOsm/kg
Identity	Identity	s47	s47	Identity Confirmed	Identity Confirmed
Quantity	Total Protein Concentration	s47	s47	s47	
Potency	Relative Potency	s47	s47		
Excipients	Matrix-A Content	s47	s47		
	Matrix-C Content		s47		
Contaminants	Sterility	Membrane Filtration USP <71> Ph. Eur. 2.6.1	On test: s47 Off test: s47	No Growth	No evidence of microbial growth found

Test Category	Quality Attribute	Methodology	Test Date	Acceptance Criteria Release	Result
	Endotoxin	Limulus Amebocyte Lysate USP <85> Ph. Eur. 2.6.14	s47	s47	< 1.00 EU/mL
Extractable Volume	Dose Delivery	USP <1>, <697> and Ph. Eur. 2.9.17	s47	**For single dose:** The content of each container, not less than 0.5 mL and not less than the sum of the nominal volume of the containers taken collectively. **For multidose container:** The volume should be such that each syringe delivers not less than stated doses.	Total Number of Doses Recovered = 10

*Descriptive language used per current method at Serum. Testing using Ph. Eur. Method pending.

5. CERTIFICATION

I herewith certify that COVID-19 Vaccine (recombinant, adjuvanted) batch N° 4302MF021 was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

Serum Quality Approver Printed Name:	s22
Serum Quality Approver Signature/Date:	DocuSigned by: s22 Signer Name: s22 Signing Reason: I approve this document s47 :06 EDT
Novavax Quality Approver Printed Name:	s22 s47 s22
Novavax Quality Approver Signature/Date:	DocuSigned by: s22 s47 s47 | 08 Signer Name: s22 Signing Reason: I approve this document Signing Time: s47 s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Laboratories Branch

Type: Biotherapeutics\BRU\Forms	**Number:** Bio-BRU-Form-67 / **Version:** 2
Owner: s22 [redacted]	**Approver** s22 [redacted]
Active: s47 [redacted]	**Review:** 23/10/2024
Title: COVID-19 Vaccine-Nuvaxovid (NVX-C0V2373) - Novavax - Protocol Checklist	

Protocol Checklist

NUVAXOVID SARS-CoV-2 rS (NVX-CoV2373) solution for injection

COVID-19 Vaccine (recombinant, adjuvanted); 10µg/mL SARS-CoV-2 rS Drug Product with 100µg/mL Matrix-M Adjuvant multi-dose vial. (10 doses of 0.5 mL).
(Aust R 35519)
Sponsor: Biocelect Pty Ltd (on behalf of Novavax)
Manufacturer: Serum Institute of India Pty Ltd

Protocol Container:	**E21-394851**	**Batch Release Container:**	**E21-394848**
CPD	**E21-312334**	**Product History**	**D22-5108910**

The protocol is received with the following:

- **Summary Information**
- **Lot Genealogy table of components**
- **Production Flowchart**
- **Starting Materials production and Testing information**
  - **Working Cell Bank**
  - **Working Virus bank**
- **Monovalent Bulk Drug Substance -** s47 [redacted]
- **Matrix A -** s47 [redacted]
- **Matrix C -** s47 [redacted]
- **Fill information**
- **Drug Product Final Fill Control Tests**
- **TSE/BSE Certification**

Reviewer:

- **Check all information has been provided and that the details concur in the checklist and the protocol.**
- **Check Tests and specifications all concur**

Working Cell Bank

Batch No.	s47 [redacted]
Date of Manufacture	s47 [redacted]

Working Virus Bank

Batch No.	s47 [redacted]	s47 [redacted]
Date of Manufacture	s47 [redacted]	s47 [redacted]

Drug Substance - Monovalent Bulk

Reviewer:

LIMS (DS TEST RESULTS)

s47 [redacted]

When entering DS results - add the DS batch number in the comments for each individual test result.

Remove the duplicated DP tests that are added as a result of adding additional test parameters.

Approved Shelf Life: s47 [redacted]

Quality Attribute	Analytical Procedure	Acceptance Criteria
Contaminant (Harvest) Mycoplasma / Spiroplasma[1]	PCR or Culture Method *USP <63> Ph. Eur. 2.6.7*	No evidence of Mycoplasma or Spiroplasma
Contaminant (Harvest) Bioburden[1] s47 [redacted] D22-5109918	Membrane Filtration *USP <61>, Ph. Eur. 2.6.12*	≤ 10 cfu/100 mL* s47 [redacted] D22-5109918
Contaminant (Harvest) Sterility[1] s47 [redacted] D22-5109918	Direct inoculation *USP <71>, Ph. Eur2.6.1*	No Growth
Contaminant (Harvest) Adventitious Agents[1]	*In Vitro* Method 4 cell lines. CPE and hemadsorption/ hemagglutination *Ph.Eur.2.6.16*	No evidence of significant adventitious viral agents
Appearance: Colour, Clarity, Visible Particles	Visual Observation *Ph. Eur. 2.2.1 / 2.2.2*	Colour: Colourless to intensity ≤ standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Practically free of visible particles
pH	Potentiometry *USP <791> Ph. Eur. 2.2.3*	6.8 - 7.6
Purity	s47 [redacted]	s47 [redacted] consistent with Assay control s47 [redacted]

Residual DNA	s47	≤ 200ng/mg total protein
Residual Infectious Baculovirus Quantification	s47	None Detected s47
Identity	s47	Identity conformed
Quantity - Total Protein Concentration	s47	s47
Potency	s47	s47
Excipients - PS80 Content	s47	s47
Bioburden (Contaminants)	Membrane Filtration *Ph. Eur. 2.6.12/USP <61>*	≤ 10 cfu/100 mL* s47 D22-5109918
Bacterial Endotoxin (Contaminants)	Endotoxin (LAL) *Ph. Eur.2.6.14*	s47

s47

Matrix A

Quality Attribute	Methodology	Acceptance Criteria Release
Color	Appearance, *Ph. Eur. 2.2.2*	B3 - B7 (Ph. Eur. reference solution)
Clarity	Appearance, Based on *Ph. Eur. 2.2.1*	Opalescent
Visible Particles	Appearance, Based on *Ph. Eur. 2.9.20*	Practically free from foreign visible particles
Identity	s47 [redacted]	Identity consistent with reference
Saponin Concentration	s47 [redacted]	s47 [redacted]
Cholesterol Concentration	s47 [redacted]	
Phosphatidylcholine (PC) Concentration		
s47 [redacted]		
Saponin Purity		
pH	Potentiometry *Ph. Eur. 2.2.3 or USP <791>*	7.0 - 7.4
Particle Size	s47 [redacted]	s47 [redacted]
Cholesterol/Saponin ratio (w/w)	s47 [redacted]	[redacted]
Phosphatidylcholine/Saponin ratio (w/w)	s47 [redacted]	[redacted]
Total Aerobic Microbial Count (TAMC) Total Combined Yeasts and Molds Count (TYMC)	*Ph. Eur. 2.6.12 or USP<61>* *Ph. Eur. 2.6.12 or USP<61>*	≤ 10 CFU/100 mL ≤ 10 CFU/100 mL
Endotoxin	*Ph. Eur. 2.6.14 or USP<85>* (kinetic)	s47 [redacted]

Matrix C

Quality Attribute	Methodology	Acceptance Criteria Release
Color	Appearance, *Ph. Eur. 2.2.2*	B3 - B7 (Ph. Eur. reference solution)
Clarity	Appearance, Based on *Ph. Eur. 2.2.1*	Opalescent
Visible Particles	Appearance, Based on *Ph. Eur. 2.9.20*	Practically free from foreign visible particles
Identity	s47 [redacted]	Identity consistent with reference
Saponin Concentration	s47 [redacted]	
Cholesterol Concentration		
Phosphatidylcholine (PC) Concentration		
s47 [redacted]		
Saponin Purity		
pH	*Ph. Eur. 2.2.3 or USP <791>*	7.0 - 7.4
Particle Size	s47 [redacted]	
Cholesterol/Saponin ratio (w/w)	s47 [redacted]	[redacted]
Phosphatidylcholine/ Saponin ratio (w/w)	s47 [redacted]	[redacted]
Total Aerobic Microbial Count (TAMC) Total Combined Yeasts and Molds Count (TYMC)	*Ph. Eur. 2.6.12 or USP <61>* *Ph. Eur. 2.6.12 or USP <61>*	≤ 10 CFU/100 mL ≤ 10 CFU/100 mL
Endotoxin	*Ph. Eur. 2.6.14 or USP <85>* (kinetic)	s47 [redacted]

Drug Product - Finished Product / Final Lot

Approved Shelf Life: 9mths when stored at 2°C to 8°C [Protect from light] Presentation - 5 mL vial		
Quality Attribute	**Analytical Procedure**	**Acceptance Criteria**
Appearance	Visual Inspection *Ph.Eur.2.2.1, 2.2.2*	Colour: Colourless to intensity ≤ standard Y5 Clarity: Clear to ≤ Ref. Suspension IV Free from visible particles.
pH	Potentiometry *(Ph. Eur. 2.2.3, USP <791>)*	6.8 – 7.6
Osmolality	Freezing Point Depression *USP <785>, Ph. Eur. 2.2.35*	NLT 240 mOsm/kg
Identity	s47 [redacted]	Identity Confirmed
Potency	s47 [redacted]	
Quantity – Total Protein Concentration		
Excipients		
Bacterial Endotoxin		
Sterility	Sterility *Ph. Eur. 2.6.1, USP <71>*	No microbial growth observed
Extractable Volume / Vial Content	Container Content Volume *USP <1> & Ph.Eur.2.9.17*	**For multidose container:** The volume should be such that each syringe delivers not less than stated dose.

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Manjari Plant

STANDARD OPERATING PROCEDURE			
Title	[redacted] DNA DETERMINATION BY [redacted]		
SOP No.	1003-0473-000	**Effective Date**	
Department	Quality Control	**Page No.**	1 of 14

APPROVALS

	E-Signature	Date and Time
Prepared by	[redacted]	[redacted] 15:54
Reviewed by	[redacted]	[redacted] 16:13
Approved by (Department Head)		
Approved by (Quality Assurance)		

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: [redacted]
[redacted]
[redacted]
NOVAVAX

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time [redacted]
[redacted]
[redacted]
Novavax Inc.

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION BY s47		
SOP No.	1003-0473-000	**Effective Date**	
Department	Quality Control	**Page No.**	2 of 14

1.0 PURPOSE:

To provide detailed instructions to determine the concentration of s47 DNA s47 present in the SARS-CoV-2rS samples s47

2.0 SCOPE:

The procedure outlined in this SOP should be followed to carry out the test for determination of the concentration of s47 DNA s47 present in the SARS-CoV-2rS Drug Substance samples at Quality Control Laboratory, s47 , Manjari.

3.0 RESPONSIBILITY(IES):

3.1 Analyst will be responsible for:

3.1.1. Carrying out the operation as outlined in this SOP.

3.1.2. Documenting the operation in analytical work sheet.

3.1.3. To complete all the training on procedures relevant to this SOP

3.2 The sectional head or his/her nominee of quality control department is responsible for:

3.2.1. To ensure that this SOP is followed and reporting any deviation from the SOP.

3.2.2. Reporting any deviation from the SOP.

3.2.3. Reviewing of raw data and audit trail, analytical work sheet, and the associated entries.

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION BY s47		
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Department	Quality Control	**Page No.**	3 of 14

4.0 DEFINITION(S): NA

5.0 SAFETY: NA

6.0 PROCEDURE:

6.1 REAGENTS, MATERIALS & EQUIPMENTS:

6.1.1 s47 [redacted]

6.1.2

6.1.3

6.1.4

6.1.5

6.1.6

6.1.7

6.1.8

6.1.9

6.1.10

6.1.11

6.1.12

6.1.13

6.1.14

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION BY s47		
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6.1.15 s47

6.1.16

6.1.17

6.1.18

6.1.19

6.1.20

6.1.21

6.1.22

6.1.23

6.1.24

6.2 PRECAUTIONS:

6.2.1 s47

6.2.2

6.2.3

6.2.4

6.2.5

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STANDARD OPERATING PROCEDURE			
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6.3 PRINCIPLE:

s47

6.4 Preparation of Controls:

6.4.1 Positive control (PC) s47 :

s47

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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6.4.2 Control Intermediate s47

s47

6.4.3 Sensitivity Control (SC) s47

s47

6.4.4 Negative Control (NC):

s47

6.4.5 Positive Control (PC) s47

6.5 Preparation of Samples:

6.5.1 s47

6.5.2

6.5.3 s47

6.5.4

6.5.5

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STANDARD OPERATING PROCEDURE			
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s47

6.5.6 s47

6.5.7

6.5.8

6.6 DNA isolation:

6.6.1 s47

6.6.2

6.6.3

6.6.4

6.6.5

6.6.6

6.6.7

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STANDARD OPERATING PROCEDURE			
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s47

6.6.8

6.6.9

6.6.10

6.6.11

6.6.12

6.6.13

6.6.14

6.6.15

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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6.6.16 s47

6.6.17

6.6.18

6.6.19

6.6.20

6.6.21

6.6.22

6.7

s47

6.8 s47

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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s47

s47

6.8.1 s47

6.8.2 s47

6.8.3

6.8.4

6.9

6.9.1

s22

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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s47

6.10 System suitability criteria:

6.10.1 s47

6.10.2

6.10.3

6.10.4

6.10.5

6.10.6

6.10.7

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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6.11 Calculations:

6.11.1 s47 [redacted]

6.11.2 [redacted]

6.11.3 [redacted]

6.11.4 [redacted]

6.11.5 [redacted]

6.11.6 [redacted]

6.12 Sample Acceptance criteria:

6.12.1 s47 [redacted]

6.12.2 [redacted]

6.12.3 [redacted]

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
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6.13 Raw data and audit trail review:

6.13.1 s47

6.13.2

6.13.3

6.13.4

6.13.5

6.13.6

6.13.7

6.13.8

6.14 REPORTING:

6.14.1 s47

6.14.2

6.14.3

6.14.4

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STANDARD OPERATING PROCEDURE			
Title	s47 DNA DETERMINATION s47		
SOP No.	1003-0473-000	**Effective Date**	
Department	Quality Control	**Page No.**	14 of 14

7.0 REFERENCES:

7.1 AMVP-0124-000 - Analytical Method Validation Protocol s47

7.2 AMVR- 0119-000 - ANALYTICAL METHOD VALIDATION REPORT s47

7.3 SOP No. 802 1417 - TOTAL DNA DETERMINATION s47

7.4 SOP No. 2001-0020 - Audit Trail Review of Computer Based System.

8.0 ASSOCIATED DOCUMENT(S):

Sr. No.	Associated Document type	Associated Document No. (Excluding Revision No.)	Title
1	FORMAT	1003-0473-F0001	s47
2	FORMAT	1003-0473-F0002	AWS FOR SPECIFICATION AND RESULTS

1 PURPOSE

The purpose of this global test method is to establish the testing requirements to determine the concentration of s47 [redacted] DNA s47 [redacted] present in SARS-CoV-2 rS Drug Substance samples s47 [redacted].

2 SCOPE

TEST TYPE	Impurity
ANALYTE	SARS-CoV-2 rS Drug Substance
MATRIX	Drug Substance: 800 – 1200 µg/mL SARS-CoV-2 rS s47 [redacted]
APPLICATION	Release
AREA	Global Quality Control
PRINCIPLE OF METHOD	s47 [redacted]

3 RESPONSIBILITIES

3.1 Novavax Global Quality Assurance/Quality Control Technical Services is responsible for the maintenance of the global test method.

3.2 Receiving site Quality Control laboratories are responsible for the local method alignment with the global test method requirements.

3.3 Novavax QA Compliance is responsible for review and approval of the global test method.

4 REAGENTS, CHEMICALS, SOLVENTS AND EQUIPMENT

4.1 Equipment:

s47 [redacted]
Multichannel and Single Channel pipettes
Vortex Mixer
Microcentrifuge

Microcentrifuge, quick spin
Microplate Shaker
Heat Block
Calibrated Thermometer
Chemical Fume Hood

4.2 Materials, Reagents, and Chemicals:

Item/Description	Manufacturer/Vendor	Part/Catalog #	Equivalent Acceptable
s47 [redacted]	[redacted]	[redacted]	
	s47 [redacted]		√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√
			√

5 HEALTH AND SAFETY CONSIDERATIONS

5.1 Refer to the hazard statements from internal safety systems and/or manufacturer(s) for handling all chemicals and reagents associated with this test method.

6 DEFINITIONS

Term	Definition
DS	Drug Substance
rS	Recombinant Spike
RT	Room Temperature
DF	Dilution Factor
dsDNA	Double-stranded deoxyribonucleic acid
HCD	Host cell DNA
IPA	Isopropyl Alcohol
NC	Negative Control
ng/mg	Nanograms of DNA per mg of protein (A280 concentration)
PC	Positive Control
R^2	Coefficient of determination
%RSD (%CV)	Relative standard deviation
SC	Sensitivity Control
s47 [redacted]	[redacted]

7 SUMMARY OF TEST METHOD AND PROCEDURE

7.1 General Information

7.1.1 All volumes may be adjusted proportionally for amount of reagent needed.

7.1.2 Allow all reagents, standard, samples and solutions to equilibrate to RT prior to use.

7.1.3 Prior to work being performed, clean area and pipettes with 70% IPA.

7.2 Reagent Preparation

REAGENT	INSTRUCTIONS
Positive Control (PC) s47 [redacted]	s47 [redacted]
Control Intermediate s47 [redacted]	[redacted]

REAGENT	INSTRUCTIONS
Sensitivity Control (SC), s47	s47
s47	
s47	s47
s47	

REAGENT	INSTRUCTIONS
s47 [redacted]	s47 [redacted]

7.3 Controls and Sample Preparation

7.3.1 s47 [redacted]

7.3.2 Negative Control (NC)

7.3.2.1 s47 [redacted]

7.3.3 Sensitivity Control (SC)

7.3.3.1 s47 [redacted]

7.3.4 Test Samples

NOTE: For test each sample, an unspiked and spiked sample is required.

7.3.4.1 Unspiked sample

7.3.4.1.1 s47 [redacted]

7.3.4.2 Spiked sample

7.3.4.2.1 s47 [redacted]

7.3.4.2.2

7.3.5 Positive Control (PC)

7.3.5.1 s47 [redacted]

7.3.6 s47 [redacted]

7.3.7

7.3.8

7.3.9 s47 [redacted]
7.3.10
7.3.11
7.3.12

7.4 s47 [redacted]

7.4.1 s47 [redacted]
7.4.2
7.4.3
7.4.4
7.4.5
7.4.6
7.4.7
7.4.8
7.4.9
7.4.10
7.4.11
7.4.12
7.4.13
7.4.14
7.4.15
7.4.16

s47 [redacted]

7.6.5 s47 [redacted]

7.7 s47 [redacted]

7.7.1 s47 [redacted]

s47 [redacted]

7.8.1 s47 [redacted].

7.8.1.1 s47 [redacted]

7.8.1.2

7.8.1.3

7.8.1.4 s47 [redacted]

8 SYSTEM SUITABILITY AND DATA ACCEPTANCE CRITERIA

System Suitability Criteria	s47 [redacted]
Data Acceptance Criteria	[redacted]

9 INTERPRETATION OF RESULTS

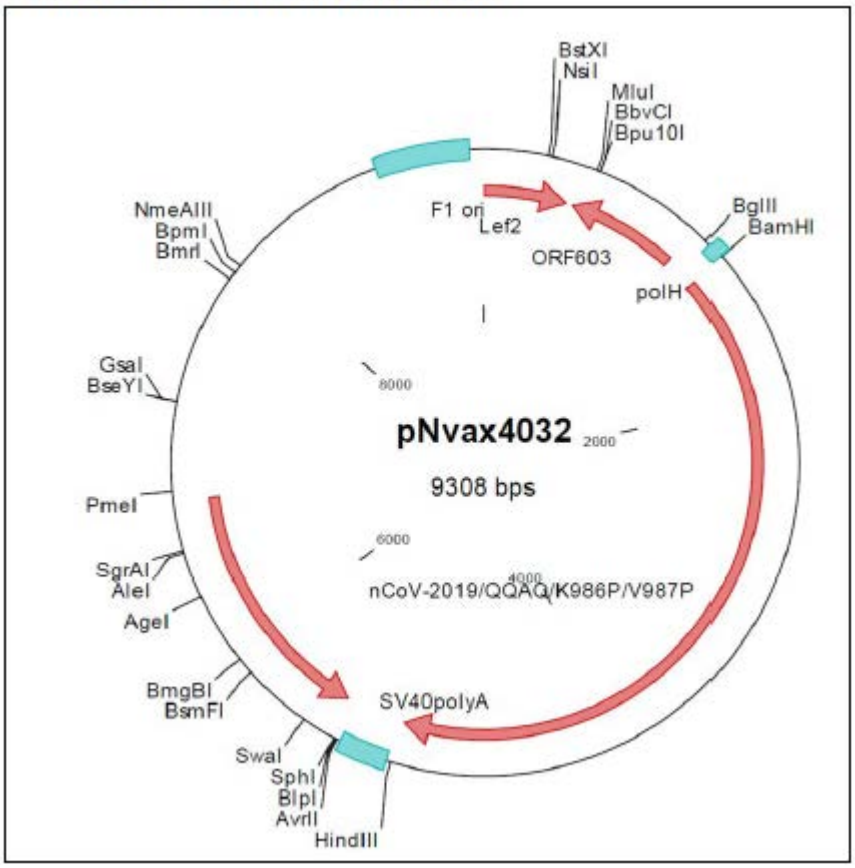
s47 [redacted]

10 REPORT

10.1 Report final DNA concentration results in ng/mg protein per Product Specification.

Plasmid Map for pNvax4032

Figure 3.2.S.2.3-4: Plasmid Map for pNvax4032



The pBAC1 transfer plasmid pNVAX5032 containing the SARS-CoV-2 rS gene and flanking sequences is shown in Figure 3.2.S.2.3-4. Beginning at 12 o'clock position on the plasmid and proceeding clockwise are the following structural elements: E.coli plasmid F1 and Lef2, the baculovirus ORF603 gene required to rescue the FlaskBacGOLD baculovirus DNA in transfected Sf9 cells as described in Section 3.2.S.2.3.3.3 Transfection of Recombinant Baculovirus Generation (P0), the AcMNPV baculovirus polyhedron promoter (polH) that controls the transcription of the rS gene (nCov-2019/QQAQ/K986P/V987P) in Sf9 cells, followed by an mRNA polyadenylation signal (SV40polyA), homologous AcMNPV gene sequence, and flanking the rS gene BglII/BamHI and HindIII restriction enzyme sites to assist in cloning the gene into the pNvax4032 E.coli transfer plasmid. Inserted in the resulting recombinant AcMNPV baculovirus BV2373 is the rS gene under transcriptional control of the

polyhedron promoter and repaired adjacent ORF603 gene required to rescue the FlashBacGOLD baculovirus DNA.